MINISTRY
OF HEALTH
•
THE NATIONAL
INSTITUTE
OF GERONTOLOGY
AND GERIATRICS
Bucharest

Romanian Journal of Gerontology and Geriatrics

CHAIRMAN OF THE EDITORIAL BOARD
Professor ANA ASLAN

1 tome 2
1981

EDITURA ACADEMIEI
REPUBLICII SOCIALISTE ROMÂNIA

EDITORIAL BOARD

Chairman:

ANA ASLAN, M.D., D.Sc., member of the Academy of the Socialist Republic of Romania, honorary member of the Academy of Medical Sciences, general director of the National Institute of Gerontology and Geriatrics

Editor-in-chief:

AL. VRĂBIESCU

Members:

M. DUMITRU, LIDIA HARTIA, VL. JUCOVSCHI, GH. APOSTOL

Editorial secretaries:

V. M. ARCAN, VL. GUSIC

ADVISORY BOARD

ANA ASLAN, C. BĂLĂCEANU, C. BOGDAN, GH. CREȚEANU, M. DUMITRU, GEORGETA ENĂCHESCU, LIDIA HARTIA, THEODORA IONESCU, ȘT. MILCU, I. MORARU, MARCELA PITIȘ, NINA SIMION, V. STROESCU, F. ȘERBAN, C. VASCAN, G. VĂGĂUNESCU, AL. VRĂBIESCU

Orders from abroad should be sent to

ILEXIM

DEPARTAMENTUL EXPORT-IMPORT PRESĂ

P. O. BOX 136—137

Str. 30 Decembrie No. 3, Telex 11226, R-79517-București, România

All manuscripts, books and journals proposed in exchange as well as all correspondence should be sent to the editorial board

ROMANIAN JOURNAL OF GERONTOLOGY AND GERIATRICS

— biannual journal —

Str. Mănăstirea Căldărușani No. 9, R-78178-București, România

Romanian Journal of
GERONTOLOGY and GERIATRICS

CONTENTS No. 1/1981

ROMANIAN J. GERONT. GERIATRICS, 1981, 2, 1, p. 3–12

DATA ON WATER AND ELECTROLYTE BALANCE IN AGING LIVING ORGANISMS

ANA ASLAN, C. T. CRĂESCU, M. DUMITRU

The National Institute of Gerontology and Geriatrics, Bucharest, Romania

Summary. The maintenance of a stable internal medium is one of the necessary conditions of body viability at all stages of ontogenesis. It is provided by constant changes of interrelated variables, water and electrolyte metabolism being one of them.

Experimental studies revealed a general tendency to a decrease in total and intracellular water, an increase in intracellular and extracellular sodium and a decrease in intracellular potassium in the tissues of aging organisms. Accumulation of intracellular sodium alongside with potassium loss result in a decreased functional ability of cells in old organisms. Sodium and potassium fluxes rates are also subjected to a significant change during the aging of tissues. The possible correlations with cell membrane changes are discussed.

Gerontology is a relatively new science focused on the study and understanding of degenerative processes specific to the time evolution of the organisms. The first gerontological researches aimed at studying the variations which take place in cells, tissues and organs. Nevertheless, most of the animal activities as a whole require coordinated activities of numerous organic systems. That is why in modern gerontology attention has been focused on the effects of aging on certain integrative processes and the mechanisms involved.

Because the complex interactions between cells and organs as well as the control mechanisms have only recently been approached by physiologists, the data are relatively meager on the effects of age on these mechanisms.

Water and electrolyte contents and balance within cells, organs and organisms are key elements in the homeostasis of living organisms. They may cause or be the effect of degenerative processes in the continuous loss of old organisms' integrative capacity. Yet, the information accumulated up to the present is rather descriptive; it includes fewer aspects of integrative physiology and systemic approach.

We shall present and discuss some literature data, trying to explain or establish correlations between experimental observations in the context of the different theories of aging.

I. TOTAL TISSULAR WATER AND ELECTROLYTE CONTENTS IN RELATION TO AGE

As most of the water amount in the body is intracellular, the evaluation of the total body water (TBW) reflects age-induced tissular atrophy. The first evaluation was done by Edelman et al. [1] for an age group from childhood

to old age. TBW was evaluated by injecting heavy water, the equilibrium distribution of which is accomplished in about 2 hrs.

There was a decrease in TBW with advancing age, calculated as percentage from the total body weight, from 61.1% in young to 54.3% in old men (Table 1).

Table 1

Total body water data as a function of age

No. subjects	Age range (years)	Weight (kg)	Total body water mean (l)	TBW/body wt. mean (%)
		In normal males		
9	10.5—15.6	46.8	27.9	59.0
34	17—34	72.6	44.1	61.1
10	35—52	79.4	43.8	55.4
6	57—86	70.7	38.1	54.3
		In normal females		
6	12—15	44.6	25.0	56.2
18	20—31	57.9	29.4	51.2
6	36—54	58.8	28.3	48.2
5	60—82	61.5	28.4	46.2

After Edelman et al. [1].

With women in the third decade TBW was 51.2% from the total body weight and dropped to 46.2% with advanced ages. Mention should be made of the low TBW percentages with women in all post-puberal age-decades, indicating the constantly higher fat content, as against men.

$$\% \text{ FATS} = 100 - \frac{\%H_2O}{0.732}$$

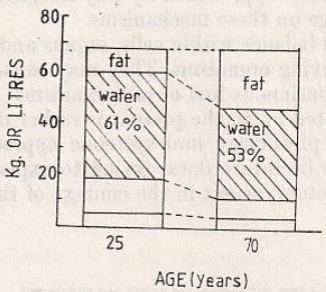


Fig. 1. — Variations with age of water and fat content in humans, after Fryer [2].

Fryer [2] found TBW to be 50—54% of the body weight with men aged 60—80; this finding tallies with Edelman et al.'s results (Fig. 1). The figure also shows the correlation between TBW decrease and the increase in fat content.

As the fat tissue, with the highest contribution to the fluctuations of the body mass in normal adults, has a low water content (14%), TBW is a good index

for the fat-free mass of the total body mass. Rathbun and Pace [3] calculated the percentage of body fats according to the formula at the top of Fig. 1. Thus, we may conclude that the decrease in the relative TBW content with advancing age reflects the increase in fat to the detriment of fat-free body mass.

Mention should be made that unlike most of the studies on the water content of the organism as a whole, which agree on its decrease, the conclusions of the studies on the water content of different tissues have been divergent, sometimes contradictory. First of all, such studies have been conducted mostly on animals, and secondly, the methods used have been quite different, hence a potential source of discrepancy.

Table 2 shows the uneven decrease in the water percentage of different parts of rabbit brain, with advancing age; there are areas such as the caudatum or thalamus where the variation is not significant [4].

Table 2

Percent water content of rabbit brain parts

	Age				
	77 days	4 years	5 years	6 years	10 years
Cortex	82.5	80.9	79.8	81.3	73.3
Caudatum	80.4	79.5	80.1	79.5	80.4
Thalamus	80.4		77.5	77.6	81.7
Cerebellum, vermis	80.9	78.3	78.2	79.9	78.9
Medulla	74.6	70.8	70.1	71.1	70.5
Cervical spinal cord	73.0		66.7	69.2	67.6

After Calloway and Dollevoet [4].

Schaub [5] finds that the water content of rat skeletal muscles decreases since birth, when it reaches 86.8%, rapidly at the beginning, slowly afterwards. At 1—2 months of age the water content reaches about 76%. In old animals, the water content increases slightly, the difference being nevertheless significant.

Goldberg et al. [6] found the highest water content of rat atrial muscle at 3 and 24 months of age; in both cases the values were significantly higher than in 1-month-old rats (Fig. 2).

Yet, the same authors reported in a different paper that no noticeable variation in the water content was detected in rat myocardium [7].

As mentioned above, the individual variations are quite large; therefore they do not allow a definite conclusion in all the studies. Fig. 3 is an example: the age-induced variations in the water content of skeletal muscle in 2 strains of white rats [8] do not significantly exceed individual variations.

Except for rat rib cartilages, all the other tissues have a relatively constant water content according to Lindner et al [9].

Inoue et al. [10] reported that in humans the water content of renal papilla increased until the fifth decade, after which it decreased. The regression with advancing age was highly significant, yet the tentative correlation with the decreased mucopolysaccharides content proved to be insignificant.

Small variations in human tissues were also reported by Simms and Stolman [11] (Table 3).

So far, we may conclude that the total water content of the whole organism decreases constantly with advancing age, whereas that of separate tissular systems presents different patterns of change, illustrating the specific pattern of organ aging

The first studies on electrolyte content based on the chemical analysis are illustrated by the results obtained by Simms and Stolman [11] (Table 3) in 1937, which pointed out increased sodium and decreased potassium contents of muscles and viscera in old subjects.

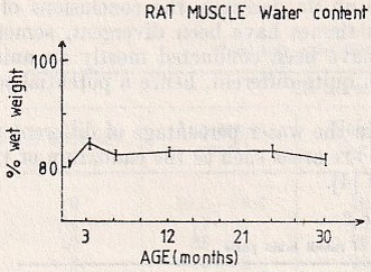


Fig. 2. — Percent water content in rat atrial muscle as a function of age, after Goldberg et al. [6].

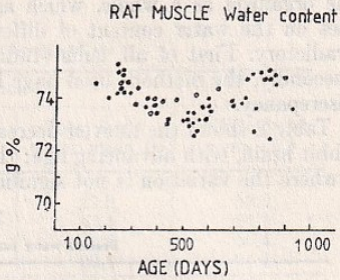


Fig. 3. — Water content in rat atrial muscle as a function of age; the values represent two different rat strains (black and open circles), after Rockstein and Hrachovec [8].

Table 3

Percent differences in weight analyses between tissues of 70-year-old and 30-year-old humans

Constituent	Kidney	Liver	Muscle	Heart	Average
H_2O	+2.6	+1.7	+0.8	−1.4	+2.0
Na	+5.0	+15.0	+62.0	+0.3	+20.0
Ca	+60.0	+4.0	+33.0	+31.0	+38.0
K	−19.0	+6.0	−7.0	−9.0	−12.0
Mg	−9.0	+17.0	−10.0	−2.5	−8.0

After Simms and Stolman. [11].

The study of electrolyte content developed rapidly since the beginning of the 6th decade owing to the technique of injecting radioactive isotopes. Using injectable ^{42}K, Moore et al. [12] demonstrated the decrease of exchangeable potassium with advancing age. Exchangeable potassium (K_e) was 45.1 mEq/kg in normal men aged 31—60 and 37.5 mEq/kg in those aged 61—90. In women the values were lower, reflecting the lower muscles/fats ratio: 34.2 mEq/kg for 31—60 years and 29.7 mEq/kg for 61—90 years.

Based on the decrease in body water content and exchangeable potassium with advancing age, Moore concluded that the cell mass of the body (skeletal muscles and visceral parenchymatous cells) decreases with age.

The technique of measuring directly the ^{40}K isotope and therefore total potassium allowed an important step forward.

^{40}K is a γ-ray emitter which represents 0.0118% of total potassium and may act as a naturally occurring tracer. A recent result [4] is presented in Table 4. It

is seen that potassium content decreased with advancing age since 18—25 years in men; subsequently the decrease was almost linear. Based on Edelman's data for body water content it is possible to calculate that K/water ratio decreased constantly during the sixth decade, suggesting that the reason of the decrease is the loss of the constant equilibrium between the muscular mass and the rest of the parenchyma. This interpretation is based on the consideration that the muscle has the highest potassium content, 153 mEq/l intracellular water.

Table 4

Total body potassium in men and women

Age (years)	Number	mEq/kg		g/kg	
		Mean	SD	Mean	SD
		Men			
18—25	27	56.1	5.54	2.18	0.204
25—35	58	53.5	4.59	2.09	0.188
35—45	33	52.7	3.40	2.06	0.169
45—55	37	49.5	4.17	1.94	0.169
55—65	42	47.8	3.89	1.87	0.158
65—85	18	43.4	3.71	1.69	0.157
		Women			
18—25	89	45.6	3.57	1.79	0.144
25—35	33	46.2	5.93	1.81	0.236
35—45	44	43.7	5.11	1.71	0.199
45—55	72	39.1	5.39	1.53	0.215
55—65	54	38.2	4.53	1.49	0.179
65—85	13	37.6	4.33	1.47	0.184

After Calloway and Dollevoet [4].

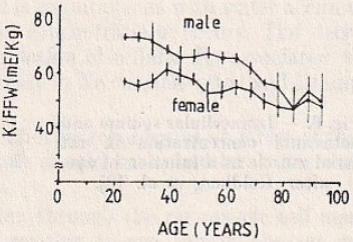


Fig. 4. — Ratio of total body potassium to fat-free mass as a function of age in males and females, after Baskin et al. [7].

Pierson et al. [13] investigated 3,083 normal subjects of all ages. Men displayed K increase with a peak of 53.8 mEq/kg body weight at 20. Subsequently, K content decreased at a rate of 0.25 mEq/kg body weight/year. In women the K/mass ratio decreased continuously since puberty because of fat gains, at a rate of 0.23 mEq/kg body weight/year, lower than in men. Using anthropometric methods to calculate fat contents, Pierson noticed that the K content of the fat-free mass decreased from 20 to 90 years of age (Fig. 4).

The longitudinal studies carried out so far yielded similar results.

Although the different methods of study raise various problems, all authors agree that total K content decreases with advancing age, earlier and more dramatically in men. K content may increase temporarily due to muscular hypertrophy occurring in the course of exercise, but after a longer period of time, K content drops by nearly 25% in men. This phenomenon may be one of the objective criteria in the aging process. Unlike the characteristic K variations, the concentration of Na ions in rat tissues varies insignificantly with advancing age (Fig. 5) [14].

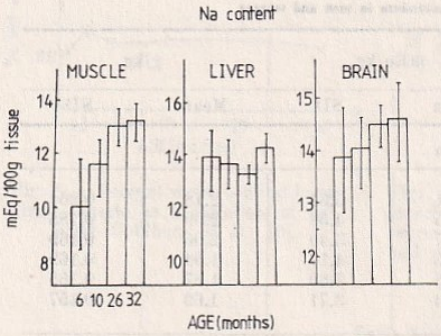


Fig. 5. — Total sodium content in different tissues of rat as a function of age, after Kuprash [14].

II. INTRA — EXTRACELLULAR BALANCE

The increase in intracellular Na noticed during the maturation of rat atrial muscle (Fig. 6), that is between 1 and 3 months of age proved significant. Between 3 and 6 months intracellular Na decreases significantly; subsequently it remains

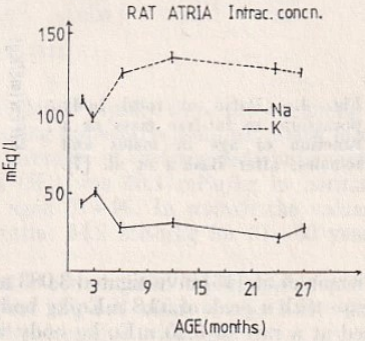


Fig. 6. — Intracellular sodium and potassium concentration in rat atrial muscle as a function of age, after Goldberg et al. [6].

constant [6]. Intracellular potassium concentration at 6 months of age is significantly different from that at 1 and 3 months. After 6 months, the concentration does not change significantly [6].

Another study on rat tissues, based on flam-photometry pointed out the decrease in intracellular K concentration simultaneously with the significant increase in Na intracellular fraction in old animals (Fig. 7) [14].

There are also contradictory results: using X-ray microanalyses, Zs.Nagy [15] found significantly higher concentrations of intracellular K in old rat liver and brain cells. Based on this study, the author advanced an original membrane hypothesis of aging involving the untoward impact of the increased intracellular ion concentration on protein synthesis.

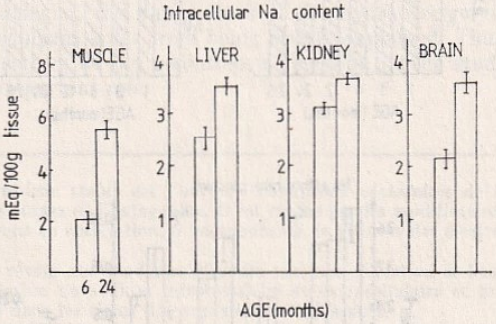


Fig. 7. — Intracellular sodium content in different tissues of rat as a function of age, after Kuprash [14].

Although the results are different to a certain extent, it may be concluded that there is an increase in intra- and extracellular Na and a decrease in intracellular K.

The variations of electrolyte balance should be correlated with the loss of cellular water with advancing age. Friedman et al. pointed out in rats the decrease in cellular water from 680.5 ml/kg dry mass at 5—7 months of age to 648.9 ml/kg dry mass at 20—25 months of age; the decrease was statistically significant [16].

Na and K extracellular accumulation is simultaneous with water accumulation, so that no important variation of plasma concentrations occurs. The decrease in cellular K parallels water loss. The accumulation of cellular Na associated with the loss of cellular water leads to a marked increase in Na concentration and an important decrease in Na transmembrane gradient.

The change of electrolyte balance can not be regarded as an effect of the variations in the cellular water content; its cause should be looked for in the variations of ion exchanges through cell membranes.

Indeed, the rate constant of Na influx through the rat muscle cell membrane has a significant tendency to increase in relation to age, except the age group of 24 months (Fig. 8) [6]. K influx does not change significantly.

Na efflux in rat myocardium was found to be multiexponential [6]. At least two components have been obtained in the course of studies with ^{22}Na: K_1 and K_2. As may be seen in Fig. 9, K_1 decreases significantly between 6 and 12 months and keeps constant until 28 months of age, whereas the rate constant K_2 has no significant variations with age. The experiments on K efflux pointed out only one rate constant which decreased significantly with advancing age.

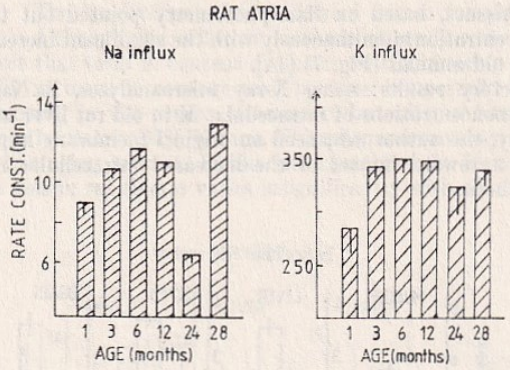


Fig. 8. — Sodium and potassium influx rate constants in rat atrial muscle as a function of age, after Goldberg et al. [6].

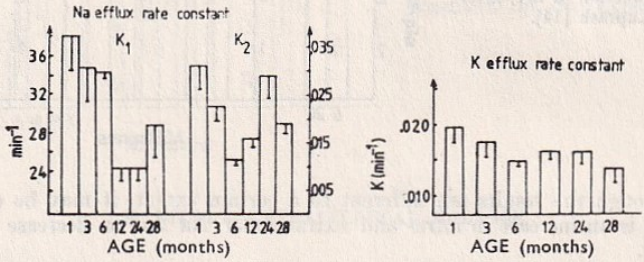


Fig. 9. — Sodium and potassium efflux rate constants in rat atrial muscle as a function of age, after Goldberg et al. [6].

III. SYSTEMIC IMPLICATIONS

The intracellular accumulation of Na associated with K loss cause the decrease in functional ability of old organisms' cells.

The change of hydro-electrolyte balance in the old organisms is not a primary, triggering phenomenon. Because of the importance of the membrane structure in maintaining the electrolyte balance between inner and outer cell spaces, the triggering phenomena should be looked for, at least partially, within the structure and functionality of the cell membranes. As pointed out in a previous study [17], one of the risk factors in aging, the free radicals, can change the composition of the biological membrane due to their enhanced reactivity, when antiradical mechanisms are less efficient. This would account for the kinetic changes in electrolyte transport.

On the other hand, the dimerization or the cross-links of biomolecules, triggered by the enhanced free radical reactivity, impair deeply the hydration of the respective biomolecules and consequently the water content and distribution in old organisms. The topic is quite interesting and worth studying.

The consequences of changes in the hydro-electrolyte balance affect, in the first place, the physiology of excitable cells (nerves, muscles) and important organs such as the myocardium. Secondly, as pointed out by Zs.Nagy [15], the intra-

cellular electrolyte concentration influences protein synthesis and may account for the low protein synthesis in old cells (particularly postmitotic). We may also speak of gerontopharmacological implications to the extent to which drugs capable of restoring functional levels are looked for. As an example mention should be made of centrophenoxine, the neuroenergizing drug which proved to influence K intracellular content of rat cortical cells [15].

The eutrophic medication (Gerovital H_3 and Aslavital) could influence the hydro-electrolyte balance due to the procaine membrane modulator effect (procaine being their major component).

Due to experimental difficulties, which could be overpassed only by developing new techniques and methodologies, the implications of the hydro-electrolyte balance on the aging of living organisms is far from being clearly explained. Thus, it remains one of the major objectives of the gerontologic research, in the study of which biophysics will play an important role.

Résumé. Le maintien d'un milieu intérieur stable est l'une des conditions nécessaires de la viabilité de l'organisme dans toutes les étapes de l'ontogenèse. Il est réalisé par les modifications continuelles des variables qui se trouvent en corrélation, le métabolisme de l'eau et des électrolytes étant l'une d'elles.

Des études expérimentales ont révélé une tendance générale vers une réduction de l'eau totale et intracellulaire, une augmentation du sodium intracellulaire et extracellulaire et une réduction du potassium intracellulaire dans les tissus des organismes vieillissants.

L'accumulation du sodium intracellulaire en même temps que la perte du potassium ont pour résultat une capacité fonctionnelle diminuée des cellules dans les organismes âgés. Le coefficient du flux de sodium et de potassium est, lui aussi, soumis à des modifications significatives au cours du vieillissement des tissus. On discute les corrélations possibles avec les modifications de la membrane cellulaire.

REFERENCES

1. I. S. EDELMAN, H. S. HELEY, P. R. SCHLOERS, D. B. SHELDON, B. J. FRUSHANSEN, G. STOLL, F. D. MOOR, *Further observations on total body water. I. Normal values throughout the life span.* Surg. Gynecol. Obstet., **99**, *1*, 1952.
2. J. H. FRYER, *Study of body composition in men aged 60 and over.* In: *Biological Aspects of Aging*, N. V. SHOCK (ed.), Columbia Univ. Press, New York, 1962, p. 52.
3. E. N. RATHBUN, A. PACE, *Studies on body composition. I. Determination of body fat by means of the body specific gravity.* J. Biol. Chem., **158**, 1945, 667.
4. N. O. CALLOWAY, P. L. DOLLEVOET, *Selected tabular material on aging.* In: *Handbook of Biology of Aging*, Van Nostrand Reinhold Co., New York, 1976, p. 666.
5. M. C. SCHAUB, *The aging of collagen in the striated muscle.* Gerontologia, **8**, *16*, 1963.
6. P. B. GOLDBERG, S. I. BASKIN, J. ROBERTS, *Effects of aging on ionic movements of atrial muscle.* Fed. Proc., **34**, 1975, 188.
7. S. I. BASKIN, P. B. GOLDBERG, J. ROBERTS, *Studies in age-related ion metabolism in rat myocardium.* In: *Exploration in Aging*, V. J. CRISTOFALO, J. ROBERTS, R. C. ADELMAN (eds.), Plenum Press, New York, 1975, p. 275.
8. M. ROCKSTEIN, J. P. HRACHOVEC, *Biochemical criteria for senescence in mammalian structure. II. Age changes in the chemical composition of rat liver and muscle: water content, defatted dry weight, total lipids and various lipid compounds.* Gerontologia, **7**, 1963, 30.
9. J. LINDNER, K. GRASEDYCK, B. SCHUTTE, M. WAGNER, M. UEBERBERG, N. DETTMER, S. BITTMANN, I. SCHULZ, *Aging of connective tissue.* 5th Eur. Symp. Basic. Res. Gerontol., Weimar, 1976, p. 219.

10. G. INOUE, T. SAWADA, M. YOSHIKAWA, *Age-related change in acid mucopolysaccharides level and water content in the papillary region of human kidneys.* Gerontologia, **19,** 1973, 73.
11. H. S. SIMMS, A. STOLMAN, *Changes in human tissue electrolyte in senescence.* Science, **86,** 1937, 269.
12. F. MOORE, K. H. OLESEN, J. D. McMURREY, H. V. PARKER, M. R. BALL, C. M. BOYDEN, *The body cell mass and its supporting environment.* W. B. Saunders, Philadelphia, 1963.
13. R. N. PIERSON Jr., D. H. Y. LIN, R. A. PHILLIPS, *Total body potassium in health: effects of age, sex, height and fat.* Am. J. Physiol., **226,** 1974, 206.
14. L. P. KUPRASH, *Electrolyte contents in erythrocytes, plasma and some organs of young and old animals.* 5th Eur. Symp. Basic Res. Gerontol., Weimar, 1976.
15. I. Zs. NAGY, *A membrane hypothesis of aging.* J. theor. Biol., **75,** 1978, 189.
16. S. M. FRIEDMAN, F. A. SCUTER, C. C. FRIEDMAN, *The distribution of water, sodium and potassium in the aged rat: a pattern of adrenal preponderence.* Gerontologia, **7,** 1963, 44.
17. C. T. CRĂESCU, *Membrane aspects of aging.* Rom. Gerontol. Days, Bucharest, 1979.

ROMANIAN J. GERONT. GERIATRICS, 1981, 2, 1, p. 13–23

L'ÉTUDE DE L'INTERVALLE R—T SUR L'ÉLECTROCARDIOGRAMME, EN EFFORT ET EN CORRÉLATION AVEC L'ÂGE

ANA ASLAN, AL. VRĂBIESCU

Institut National de Gérontologie et Gériatrie, Bucarest, Roumanie

Résumé. Des sujets appartenant à deux groupes d'âge, 18—39 ans et 60—84 ans, ont été investigués, durant 3 minutes, avec le même effort modéré, à l'échelle (épreuve de Master modifiée).

On a enregistré l'électrocardiogramme (une dérivation précordiale) au repos, pendant l'effort et les 80 secondes qui suivent. On a déterminé la durée Rp—Tp (durée Rpointe—Tpointe) et Rp—Tp% (durée Rp—Tp par rapport à la durée du cycle cardiaque) avec la fréquence cardiaque.

Au cours de l'effort, chez les personnes âgées, l'allongement Rp—Tp% a lieu presque en même temps que chez les jeunes, bien que l'augmentation de la fréquence cardiaque y soit plus lente, le steady-state se stabilisant après 140 secondes (par rapport à 20 secondes chez les jeunes). Après être arrivé au maximum d'allongement (40,4%) la durée Rp—Tp% se maintient à ce niveau encore 60 secondes (tandis que chez les jeunes elle commence à se raccourcir sitôt après avoir touché le maximum) et le raccourcissement qui suit est seulement de 18,1% (par rapport à 46,7% chez les jeunes).

Dans la période de récupération, la fréquence cardiaque ne retrouve pas au cours de 80 secondes le niveau antérieur à l'effort et la durée Rp—Tp se raccourcit plus lentement que chez les jeunes.

Quant à la dynamique cardiaque, la durée Rp—Tp correspondant à la systole isométrique et à la phase d'éjection rapide, on peut considérer que les modifications mentionnées reflètent la diminution de l'efficience systolique ventriculaire chez les personnes âgées, évidente surtout au cours de l'effort.

Les principales modifications relevées par les recherches concernant la dynamique cardiaque chez les personnes âgées, portent sur la durée de la systole mécanique et sur le volume systolique. Dal Palù et coll. [1], après avoir effectué des enregistrements simultanés de l'électrocardiogramme, sphygmogramme carotidienne et phonocardiogramme, concluent que le prolongement de la durée de la systole mécanique est due à l'allongement de la systole isométrique et de la phase ventriculaire rapide, composantes de la systole isotonique, dont la durée, en ensemble, ne se modifie pas. Les auteurs attribuent ces modifications de l'activité mécanique du cœur sénile autant aux altérations du Windkessel que surtout à la méiopragie fonctionnelle de la fibre miocardique.

Selon Morpurgo [2], l'accroissement de la durée de la systole mécanique est due en exclusivité à l'allongement de la phase de contraction isotonique.

Michel [3] a décrit, aussi, l'allongement de la durée de la systole mécanique chez les âgés, et Strandell [4] remarque que l'allongement coïncide au raccourcissement du volume systolique et du travail ventriculaire gauche relevés par Brandfonbrener et coll. [5].

La diminution du volume systolique chez les âgés a été aussi constatée par Weiss et coll. [6], dans une étude portant sur 37 sujets au-dessous de 30 ans et au-

dessus de 60 ans, dont on a déterminé la courbe de dilution du bleu Evans, injecté intraveineux, à l'aide d'un oxymètre Atlas, couplé à l'enregistreur Atlas 4.

L'exploration hémodynamique effectuée par Granath et coll. [7], par le cathétérisme du cœur droit et l'enregistrement simultané de la la pression artérielle directe, a montré que, chez les âgés, le volume systolique (mesuré par la méthode Fick directe) diminue de 23%, la pression systolique dans l'artère brachial est plus grande et la pression systolique et dyastolique dans l'artère pulmonaire est plus basse que chez les jeunes.

Quant à l'accroissement du temps d'éjection aortique avec l'âge, accentué chez les coronariens, Simonson et Nakagawa [8], le considère en liaison avec les phénomènes ischémiques ventriculaires qui influencent la contraction isométrique ventriculaire.

Harrison et coll. [9] relève l'allongement avec l'âge de la période de contraction isovolémique de même que la phase de relâchement isométrique. Le fait que le temps d'éjection croît, au lieu de se raccourcir, pendant la diminution du volume, est considére par les auteurs, comme une indication de la réduction chez les âgés de la quantité moyenne d'éjection.

En effet, les méthodes utilisées jusqu'à présent, dans l'investigation de la dynamique cardiaque ont apporté des données concluantes afin de justifier la recherche de nouvelles possibilités de les faire remarquer par des moyens plus accessibles et à large utilisation. C'est le but de notre recherche.

MATÉRIEL ET MÉTHODE

Le travail a porté sur 30 sujets sains du point de vue clinique, appartenant à deux groupes d'âge, à savoir 15 jeunes de 18—39 ans et 15 âgés de 60—84 ans.

La preuve est faite pendant la matinée, avant 11 heures. On recommande aux sujets de ne pas faire d'efforts avant la preuve de laboratoire.

On commence par l'enregistrement de l'électrocardiogramme (12 dérivations) en positions supine, afin de déceler d'éventuels troubles de rythme ou de conduction, qui rendraient impossible la preuve. Ensuite, on pose une électrode précordiale des deux côtés du stern, au niveau de l'espace 4 intercostal (à 15 cm distance l'un de l'autre) le connectant à un appareil électrocardiographique à un seul canal, dans la première dérivation standard.

Après 15 minutes de repos en position assis, on fait l'enregistrement de l'électrocardiogramme avec la vitesse de roulement du papier 10 mm/s. Le sujet exécute ensuite, à une échelle double à 2 marches de 22,5 cm chacune, un exercice de 3 minutes avec le rythme de 12 montées et descentes par minute (méthode Master modifiée). Le rythme est établi par un métronome au rythme de 50/minute. L'enregistrement de l'électrocardiogramme se fait continuellement dès le début de l'exercice. À la fin de l'exercice, le sujet revient à la position assise et l'enregistrement continue encore 80 secondes.

Afin de pouvoir interpréter les données obtenues, on va mesurer la fréquence cardiaque et l'intervalle Rp-Tp, à savoir:

— on établit, avant l'effort, sur 18 intervalles R—R consécutifs, la fréquence cardiaque de repos, ainsi que la durée Rp-Tp rapportée en pourcentage par rapport au cycle cardiaque correspondant;

— pendant l'effort et la période de récupération on fait les mêmes déterminations à raison de 6 cycles cardiaques pour toutes les 10 secondes d'intervalle,

mesurées sur l'électrocardiogramme (18 intervalles de 10 secondes chacun pendant la période d'effort et 8 intervalles de 10 secondes chacun pendant la période de récupération).

A l'aide de ces données on fait le graphique de l'évolution de la fréquence cardiaque, de la durée Rp-Tp et Rp-Tp% par rapport au cycle cardiaque pendant la preuve d'effort et la période de récupération et on fait le calcul statistique de la signification des différences entre les jeunes et les âgés.

RÉSULTATS OBTENUS

1. LA FRÉQUENCE CARDIAQUE

a) Chez les jeunes, de la moyenne de 73,3/minute, en repos, la fréquence croît brusquement jusqu'à un maximum de 112/minutes en 20 secondes, après quoi elle se maintient en limites rapprochées jusqu'à la fin de l'exercice (steady-state).

Pendant la période de récupération, la fréquence diminue, de sorte qu'à 50 secondes revient au niveau antérieur à l'exercice, mais ensuite elle diminue davantage (fig. 1, tableau 1).

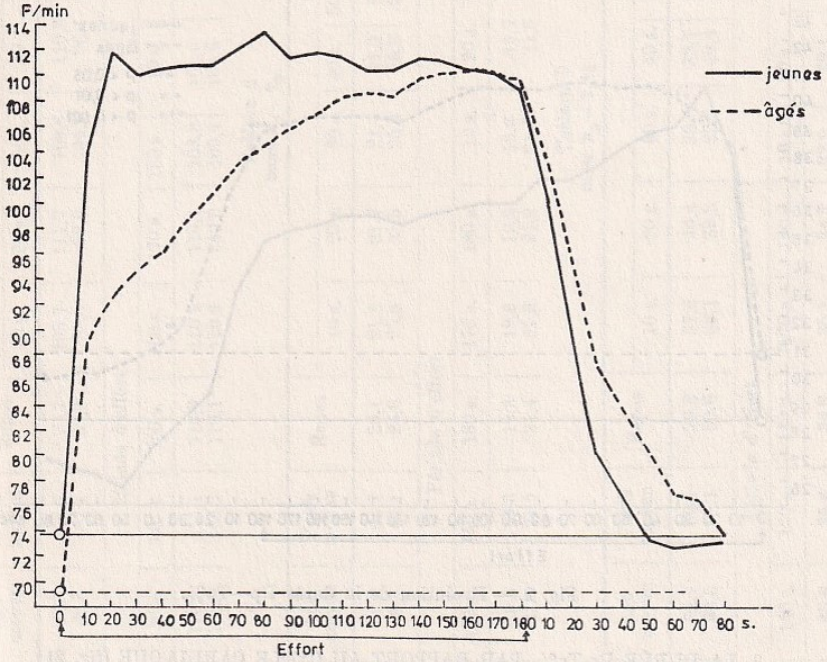


Fig. 1. — Evolution de la fréquence cardiaque.

b) Chez les personnes âgées, de la moyenne de 69,3/minutes en repos, la fréquence augmente plus lentement que chez les jeunes, ainsi que la période steady-

state commence après 140 s. Le maximum est de 110/minutes, rapproché aux jeunes. Par rapport au niveau initial, l'accroissement est de 58,8%, tandis que chez les jeunes il est de 51,8%. Après l'effort, la fréquence diminue lentement, de sorte qu'à 80 s, elle est encore au-dessus du niveau initial.

2. LES INTERVALLES Rp-Rp ET Rp-Tp

L'intervalle Rp-Rp a une évolution identique à la fréquence cardiaque, mais dans le sens contraire.

En ce qui concerne Rp-Tp on fait les constatations suivantes:

Chez les jeunes, la durée en repos est de 23,1 c/s., et chez les personnes âgées elle est de 25,6 c/s. Pendant l'effort toutes les deux diminuent, le minimum réalisé à 180s étant de 19,2 c/s. chez les jeunes et de 21,2 c/s. chez les âgés. (Tableau 2).

Après l'effort toutes les deux tendent à revenir au niveau initial, mais sans y arriver jusqu'à 80 secondes.

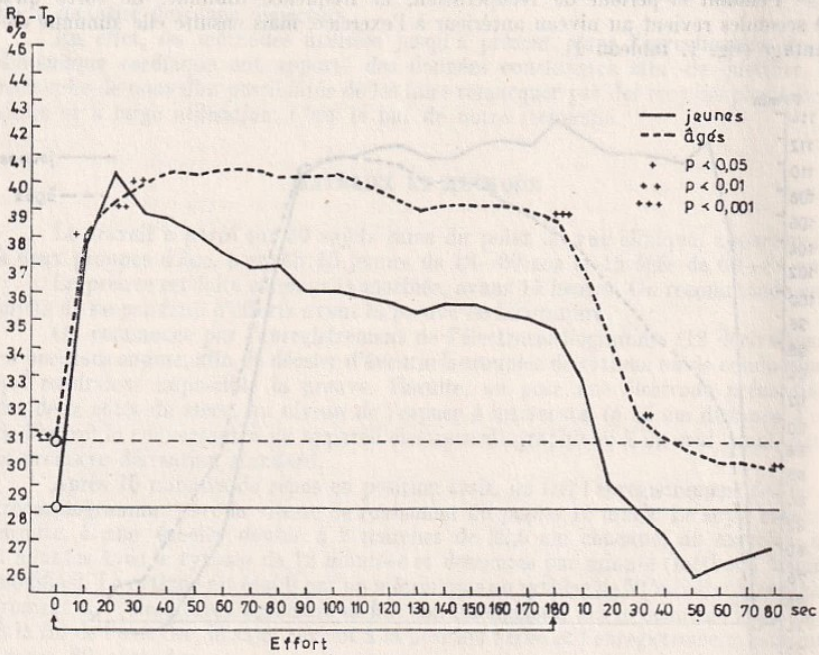


Fig. 2. — Evolution de la durée Rp—Tp%.

3. LA DURÉE Rp-Tp%, PAR RAPPORT AU CYCLE CARDIAQUE (fig. 2)

a) Chez les jeunes, de la moyenne de 28,2% en repos, la durée Rp-Tp% s'allonge rapidement, en arrivant à un allongement maximum 40,4% à 20 s. Un raccourcissement progressif suit, en arrivant jusqu'à la fin de l'exercice à 46,7%

Tableau 1

Fréquence cardiaque

Le groupe	Age moyen	Poids moyen	Repos	Période d'effort									
				10 s.	20 s.	30 s.	40 s.	50 s.	60 s.	70 s.	80 s.	90 s.	100 s.	110 s.
Jeunes	22,7	66,7	73,7	103,7	111,7	109,9	110,3	110,6	110,7	112,0	113,2	111,2	111,6	111,3
Agés	69,5	67,1	69,3	88,8	92,6	94,7	96,1	98,7	100,8	103,2	104,3	105,8	106,8	108,2

Période d'effort							Période de repos						
120 s.	130 s.	140 s.	150 s.	160 s.	170 s.	180 s.	10 s.	20 s.	30 s.	40 s.	50 s.	60 s.	70 s.	80 s.
110,2	110,3	111,1	110,9	110,2	110,1	108,8	101,0	88,8	81,0	76,8	73,2	72,5	72,7	73,0
108,5	108,3	109,7	110,1	110,3	110,0	109,7	103,6	95,7	87,3	83,9	80,1	77,0	76,3	73,7

Tableau 2

Durée $R_p - T_p$

Le groupe	Age moyen	Poids moyen	Repos	Période d'effort										
				10 s.	20 s.	30 s.	40 s.	50 s.	60 s.	70 s.	80 s.	90 s.	100 s.	110 s.	120 s.
Jeunes	22,7	66,7	23,1	21,8	21,7	21,4	21,2	20,8	20,3	19,8	19,7	19,6	19,5	19,4	19,5
Agés	69,5	67,1	25,6	25,8	25,5	25,4	25,3	24,6	24,9	23,7	23,2	22,9	22,7	22,2	21,9

Période d'effort						Période de repos							
130 s.	140 s.	150 s.	160 s.	170 s.	180 s.	10 s.	20 s.	30 s.	40 s.	50 s.	60 s.	70 s.	80 s.
19,3	19,3	19,3	19,3	19,2	19,2	19,6	19,7	20,2	20,7	21,2	21,7	22,0	22,1
21,7	21,5	21,5	21,4	21,3	21,2	21,4	21,6	21,8	22,0	22,7	23,3	23,6	24,1

Tableau 3

Durée $R_p - T_p$%

Le groupe	Age moyen	Poids moyen	Repos	Période d'effort										
				10 s.	20 s.	30 s.	40 s.	50 s.	60 s.	70 s.	80 s.	90 s.	100 s.	110 s.	120 s.
Jeunes	22,7	66,7	28,2	37,6	40,4	38,9	38,7	38,2	37,4	36,9	37,0	36,1	36,1	35,9	35,7
Agés	69,5	67,1	30,6	38,1	39,3	39,9	40,4	40,3	40,5	40,5	40,2	40,2	40,3	40,0	39,5

Période d'effort						Période de récupération							
130 s.	140 s.	150 s.	160 s.	170 s.	180 s.	10 s.	20 s.	30 s.	40 s.	50 s.	60 s.	70 s.	80 s.
35,3	35,6	35,6	35,3	35,1	34,7	32,9	29,1	28,1	27,2	25,7	26,1	26,4	26,7
39,0	39,2	39,2	39,2	39,0	38,7	36,9	34,3	31,5	30,7	30,2	29,8	29,8	29,6

de l'allongement maximum produit à 20s. Après l'exercice, la durée Rp-Tp% diminue rapidement, de sorte qu'à 30s elle se situe sous le niveau initial (Tableau 3).

b) Chez les âgés, de la moyenne de 30,6% en repos, la durée Rp-Tp% s'allonge presque aussi rapidement que chez les jeunes (en 40 s) jusqu'à la limite maximum de 40, 5%. Mais à l'encontre des jeunes, la durée Rp-Tp% ne commence à se raccourcir qu'après 110 s. d'effort, de même que la diminution qui suit jusqu'à la fin de l'exercice est seulement de 18,1% de l'allongement maximum à 40 s.

Pendant la période de récupération, la durée Rp-Tp% diminue plus lentement que chez les jeunes et à partir de 50 s se raccourcit peu sous le niveau initial.

DISCUSSIONS

Les recherches concernant la durée de la systole électrique ventriculaire sur l'électrocardiogramme par rapport à l'âge ont été faites en général en conditions de repos par le mesurage de l'intervalle Q—T. Fedele [11], Löhr et Tillmans [12], Lubich et Facci [13] considèrent l'allongement Q-T une caracteristique des âges avancés. Selon l'opinion de Crosetti et coll. [14], Dagnini [15], l'allongement serait rencontré en 49,2 respectivement 44% des cas. D'autres auteurs trouvent des allongements même plus modestes [Garello E. et coll. (16)], et selon Dal Palù et coll. [1], Q—T croît seulement après l'âge de 80 ans.

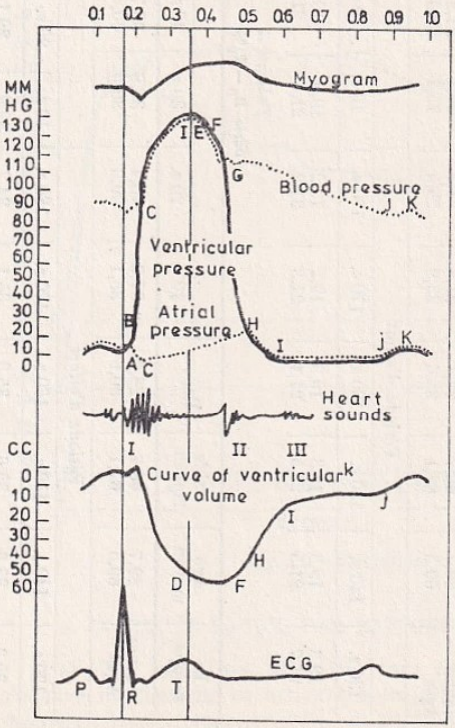


Fig. 3. — La corrélation de l'intervalle Rp — Tp avec le miogramme ventriculaire, les pressions aortique, ventriculaire et artérielle, les bruits du cœur, le volume ventriculaire et l'électrocardiogramme (selon Wiggers, cité de A. A Luisada, en: Cardiology, tome I, p. 2—75. Ed. Mc Graw-Hill, New York, 1959).

La principale cause de ces discordances consiste dans la technique de mesurer Q-T et surtout dans la détermination précise de la fin de l'onde T. L'hypovoltage de cette onde et la superposition de l'onde U sur sa pente descendante, surtout chez les âgés, mènent à des difficultés de calcul. En outre, il peut intervenir des erreurs dans le mesurage exact du début de l'onde Q, en fonction de la position du cœur.

Pour éviter ces inconvénients, nous nous sommes proposé de prendre des repères plus exacts dans le mesurage de la durée de la systole électrique, à savoir les pointes des ondes R et T.

A l'avantage technique offert par le mesurage de l'intervalle Rpointe-Tpointe (Rp—Tp) dans l'étude de la durée de la systole électrique, on ajoute sa signification pour la dynamique cardiaque. L'analyse des phases composant la systole électrique (fig. 3) montre que cet intervalle comprend entièrement la systole isométrique et la phase d'éjection rapide [17] (qui représente 2/3 du volume systolique), toutes les deux prolongées chez les âgés [1, 8, 9].

Le déplacement vers la droite de la pointe de l'onde T, observé chez les sujets de plus de 60 ans [1], fait augmenter l'intérêt pour la recherche de l'intervalle Rp—Tp.

À la suite des résultats obtenus par les mesurages de l'intervalle Rp—Tp, par rapport à la fréquence cardiaque, on a apprécié qu'une représentation plus suggestive de la corrélation entre la durée et l'efficience de la systole électrique peut être obtenue par un pourcentage (%) par rapport à la durée du cycle cardiaque (Rp—Tp%).

On a essayé par conséquent, de souligner le rôle fonctionnel du temps systolique dans la dynamique cardiaque. Il est connu le fait que chez les jeunes, sains du point de vue clinique, un temps systolique court est l'expression électrocardiographique d'une systole rapide et vigoureuse [18], après un bon remplissage diastolique. Elle est dépendante de l'état morpho-fonctionnel du myocarde, de l'équilibre neuro-végétatif et de l'ensemble fonctionnel hémodynamique.

L'allongement significatif ($p < 0{,}001$) chez les âgés, en repos, de l'intervalle Rp-Tp et, à la suite de la corrélation à la durée du cycle cardiaque, du Rp-Tp% correspond aux données obtenues par les auteurs qui décrivent un allongement de Q—T avec l'âge [1, 11, 16].

De même, c'est en concordance avec l'allongement de la systole mécanique signalé par ceux qui ont étudié sa durée par l'intermédiaire des explorations hémodynamiques complexes [2, 3, 8, 9]. Ce résultat coïncide aussi à la baisse du volume systolique chez les âgés, relevée par Brandfonbrenner et coll. [5] et Granath et coll. [7].

En conditions d'effort égal comme intensité et durée, le comportement différent de la dynamique cardiaque chez les âgés par rapport aux jeunes se révèle éloquent en ce qui concerne l'évolution de l'intervalle Rp-Tp et surtout par la corrélation de 3 éléments: la fréquence cardiaque, l'intervalle Rp-Tp% et leur évolution en temps (fig. 4). Les deux boucles tracées ont des formes différentes due à l'évolution de Rp-Tp% chez les âgés.

L'allongement plus grand de Rp-Tp% par rapport à la fréquence cardiaque pendant les 40 premières s de l'exercice et la capacité beaucoup plus diminuée de raccourcir la durée dans la période steady-state, 18,1% par rapport à 46,7% chez les jeunes (différence significative à $p < 0{,}001$), sont les principales caractéristiques chez les âgés pendant l'effort.

L'allongement augmenté de Rp-Tp% au cours de l'exercice, chez les âgés, correspond à la diminution des volumes systoliques, décrite par Durand et coll. [19] par des mesurages radiocardiographiques ainsi qu'aux recherches radiologiques

de Friedman [20], par la cardiométrie et l'enregistrement des dimensions ventriculaires faites par Rushmer [21], ou à l'étude de Cournand et coll. [22], concernant les courbes de dilution des colorants et des radio-isotopes.

La diminution prolongée, pendant toute la durée de l'exercice du temps diastolique, influence d'une manière défavorable la circulation dans le système coronaire, où le débit est maximum en diastole et nul, même rétrograde dans une certaine période de la systole [15]. C'est une cause possible de la dénivellation du segment S-T après l'effort, décrite par Master et Rosenfeld [16, 17, 18] et que nous avons trouvée dans 4 cas chez les âgés.

En ce qui concerne la période de récupération, à l'encontre des jeunes, chez les âgés la récupération est plus lente, le raccourcissement de l'intervalle Rp-Tp% survenant plus doucement.

La signification de ces modifications décrites chez les âgés, peut être déduite de l'étude comparative des données concernant l'intervalle Rp-Tp% (correspondant à la systole isométrique et à la phase d'éjection rapide), par rapport à l'évolution

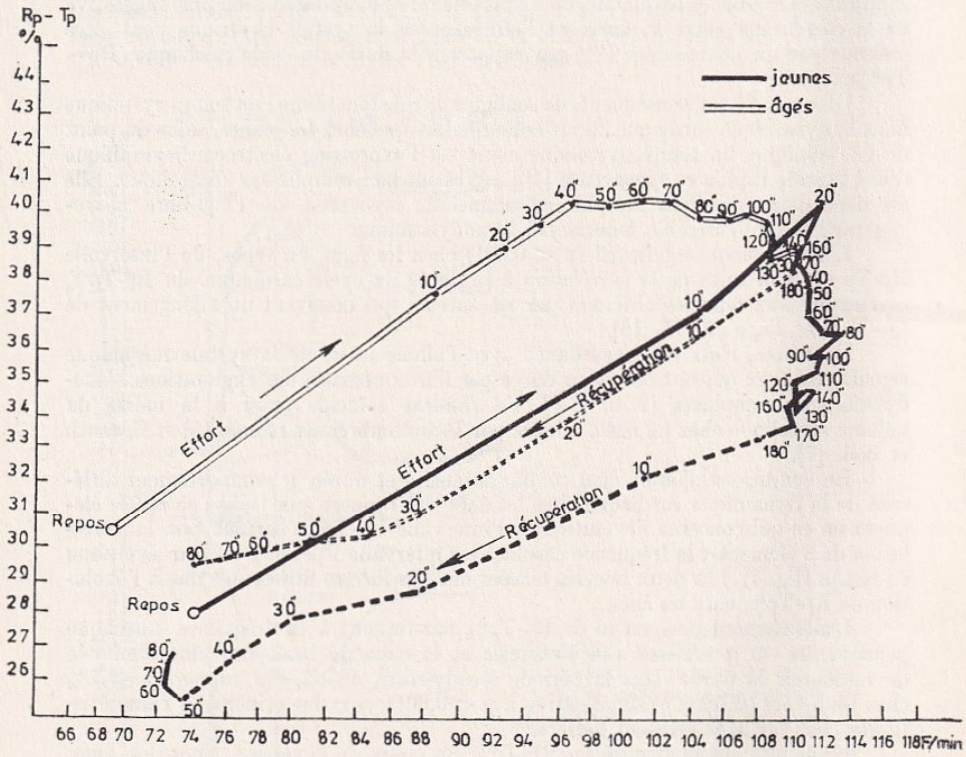


Fig. 4. — Evolution en temps de la durée Rp—Tp% et de la fréquence du cœur.

de la dynamique cardiaque chez les jeunes, en conditions d'effort. Chez les jeunes, l'allongement Rp-Tp% et la diminution du volume ventriculaire arrivent au maximum dans les 20—30 premières s après le début de l'exercice musculaire. On sait que, dans cette période, l'augmentation du volume cardiaque est réalisé seulement par l'accélération de la fréquence du cœur.

Ultérieurement, la réduction partielle de l'allongement Rp-Tp% a la signification d'une amélioration de l'efficience systolique et correspond à la période décrite par Durand et Martineaud [23] où le volume systolique augmente surtout grâce au sang résiduel ventriculaire (le résidu postsystolique diminue). L'augmentation du volume cardiaque dans cette deuxième phase est réalisée autant par la fréquence cardiaque élevée que par un volume systolique amélioré par l'utilisation d'une certaine partie du volume systolique résiduel. Il se produit aussi, un remplissage diastolique plus rapide et plus efficient, en raison de l'augmentation de la vitesse de circulation du sang et de l'augmentation du retour veineux. Il est probable, que l'augmentation du retour veineux, par la sollicitation qu'il exerce sur la fibre du myocarde, contribue à l'augmentation de la tension de contraction, et donc au raccourcissement de la systole isométrique, ainsi qu'au raccourcissement de la phase d'expulsion rapide, constatés par nous en mesurant la durée Rp-Tp% pendant la seconde partie de l'effort.

Un autre facteur qui y contribue est l'accroissement du tonus nerveux symphatique pendant l'effort, ce qui détermine l'accélération de la fréquence du cœur et un accroissement de l'excitabilité et de la force de contraction du myocarde.

Le ralentissement rapide de la fréquence cardiaque chez les jeunes, après l'arrêt de l'effort, est suivi d'un raccourcissement important au-dessous du niveau de repos, de l'intervalle Rp-Tp%, ce qui suppose une efficience systolique plus grande et donc une récupération rapide. Il se produit probablement, l'augmentation du volume systolique, avec son retour à la valeur antérieure à l'effort, la dépassant même temporairement.

Du point de vue étiopathogénique, les modifications de la fréquence cardiaque, de la durée de la systole isométrique et de la phase d'éjection rapide (l'intervalle Rp-Tp) chez les âgés, en conditions de repos et d'effort, sont déterminées par plusieurs facteurs, dont on mentionne:

— l'involution de la structure myocardique due à l'âge et aux phénomènes ischémiques ventriculaires, qui engagent la diminution de l'excitabilité et de la force de contraction;

— une certaine prévalence du tonus parasympathique chez les âgés, qui influence les fonctions inotrope et tonotrope du cœur;

— les altérations Windkessel produites par l'âge, ce qui détermine la réadaptation de la dynamique cardiaque.

La réponse plus lente de la fréquence cardiaque, au cours de l'exercice chez les âgés, peut dépendre aussi de l'état d'inertie des processus nerveux que nous avons présentés dans d'autres recherches [26, 27].

Par sa simplicité et sa signification pour la recherche de la dynamique cardiaque, cette preuve pourrait être utilisée en tant que moyen d'investigation, afin de déceler certains phénomènes d'involution accélérée au niveau du cœur et de faciliter les indications thérapeutiques.

Pour conclure, le mesurage sur l'électrocardiogramme — en repos, à l'effort et pendant la période de récupération — de la durée systolique isométrique et de

la phase rapide d'éjection systolique, par rapport à la durée du cycle cardiaque (Rp-Tp%), met en évidence certaines modifications de la dynamique cardiaque avec l'âge.

La preuve s'applique aisément, en nécessitant un électrocardiographe habituel, et l'effort modéré est bien supporté jusqu'aux âges avancés.

Les auteurs remercient le prof. F. Bourlière, le Directeur du Centre de Gérontologie de Paris et sa collaboratrice Dr. Hélène Cendron, pour le concours accordé à la réalisation de ce travail.

Summary. Investigations were carried out on two age groups: 18—39 and 60—84, subjected to stepping up and down stairs (modified Master test), for 3 minutes.

The electrocardiogram (precordial lead) was recorded at rest, during work and in the following 50 seconds after work. The duration of the $R_p - T_p$ interval (duration of $R_{peak} - T_{peak}$) and of the $R_p—T_p\%$ interval (duration of $R_p - T_p$ interval in percent of the duration of the cardiac cycle) in terms of the heart rate was registered.

During work, in the aged, $T_p—T_p\%$ is prolonged at almost the same moment as in the young age group, although increase in the heart rate takes place more slowly, the steady state being established after 140 seconds (as compared to 20 seconds in youth). After maximum lengthening (40.4%), the duration of $R_p—T_p\%$ is maintained at the same level another 60 seconds (in youth this takes place much sooner) and the shortening that follows is of only 18.1% (as compared to 46.7% in youth).

In the recovery period the heart rate does not return to initial values within 80 seconds and the duration of $R_p—T_p$ becomes shorter more slowly than in youth.

As regards the dynamics of the heart, the duration of $R_p—T_p$ corresponding to the isometric systole and rapid ejection phase, the changes described may be considered to reflect diminution in the ventricular efficiency of the heart in the aged, that is made evident especially in the course of work.

BIBLIOGRAPHIE

1. C. DAL PALU, F. GOBBATO, B. DE BIASIO, E. VENDRANE, *Aspetti emodinamici ed elettrocardiografici nell'età senile*, G. Geront., **VI,** *6*, 1958, 385—428.
2. M. MORPURGO, *Aspetti fisiopatologici del cuore senile*, G. Geront., *6*, 1958, 683—702.
3. D. MICHEL, *Über die Alternsenhängigkeit der dynamischen Herzzeitwerte*, Z. Alternsforsch., **14,** 1960, 282—292.
4. T. STANDELL, *Mechanical Systole at Rest, During and After Exercise in Supine and Sitting Position in Young and Old Men.*, Acta physiol. scand., **61,** 1964, 279—298.
5. M. BRANDFONBRENER, M. LANDOWNE, N. W. SCHOCK, *Changes in Cardiac Output with Age, Circulation*, **12,** 1955, 537.
6. ST. WEISS, C. STREIANU, E. COBILANSCHI, *Considérations concernant les modifications hémodynamiques chez les âgés, en conditions normales et pathologiques*, Méd. interne (Buc.), **XVII,** *1*, 1965, 75—80.
7. A. GRANATH, B. JONSSON, T. STRANDELL, *Studies on the Central Circulation at Rest and During Exercice in the Supine and Sitting Body Position in Old Men.*, Acta med. scand., **169,** 1961, 125.
8. E. SIMONSON, K. NAKAGAWA, *Effect of Age on Pulse Wave Velocity and "Aortic Ejection Time" in Healthy Men with Coronary Artery* Disease, Circulation, **20,** *1*, 1960, 126—129.
9. T. R. HARRISON, K. DIXON, R. O. RUSSEL, P. S. BIDWAI, H. N. COLEMAN, *The relation of Age to Duration of Contraction, Ejection and Relaxation of the Normal Human Heart*, Amer. Heart. J., **67,** 1964, 189.

10. F. BOURLIÈRE, H. CENDRON, AL. VRĂBIESCU, J. VALLERY-MASSON, *Investigation of Cardiovascular Adaptation to Effort of Old Subject*, Biol. Clin. Med., 7th Intern. Congr. of Gerontology, Viena, 26. VI — 2.VII.1966, Proceedings, vol. 2, 377—379.
11. R. FEDELE, *Richerche cliniche sulla durata della sistole ventriculare*, Arch. scand. Med., **70,** 1940, 515.
12. H. LÖHR, H. TILLMANS, Cité de Dal Palù (1).
13. T. LUBICH, M. FACCI, *La sistole elettrica. 1° Valutazione clinica e metodi di calcolo*, Folia cardiol., **14,** 1955, 247.
14. L. CROSETTI, G. RANDONE, M. SCHIAVINE, *Cité de Dal Palù* (1).
15. G. DAGNINI, *L'elettrocardiogramma nell'età senile. Variabilità individuale*, Arch. Patol. Clin. Med., *13*, 1933, 78.
16. E. GARELLO, G. BERTOLIA, E. CAVIGHIA, *Ricerche sulla durata della sistole elettrica nell'età senile*, Arch. E. Maragliano di Patol. Clin., **14,** *4*, 1958, 859—866.
17. A. A. LUISADA, *Cardiology*, vol. I, *An Encyclopedia of the Cardiovascular System*, McGraw-Hill, New York, 1959, p. 2—75.
18. R. F. RUSHMER, *Cardio-vascular dynamics*, Saunders, Philadelphia-Londra, 1961.
19. J. DURAND, J. P. MARTINEAUD, *Commande de l'activité cardiaque*, Med. Thorac., **20,** *3*, 1963, 129—151.
20. A. M. MASTER, E. T. OPPENHEIMER, *A Simple Exercise Tolerance Test for Circulatory Efficiency with Standard Tables for Normal Individuals*, Amer. J. Med. Sec., *177*, 1929, 233.
21. A. M. MASTER, I. ROSENFELD, The "Two-Step" Exercice Test Brought Up to Date, N. Y. State J. Med., **61,** *11*, 1961, 1850—1858.
22. A. M. MASTER, I. ROSENFELD, *Monitored and Post-Exercise Two-Step Test*, J. Amer. Med. Ass., **190,** *9*, 1964, 494.
23. J. DURAND, L. DONATO, J. O. PARKER, D. F. ROCHESTER, A. COURNAND, *Tentative de mesure séparée des volumes de sang présents dans les deux ventricules*, Arch. Sci. Physiol., **15,** 1961, 55—78.
24. C. E. FRIEDMAN, *The Residual Blood of the Heart. A Clinical X-ray and Pathologico-Anatomical Study*, Amer. Heart. J., **39,** 1950, 397—404.
25. A. COURNAND, *Relation of Cardiac Output to Peripheral Vascular Adjustment*, Josiah Macy Jr. Foundation, New York, 1950, 203—236.
26. AL. VRĂBIESCU, C. ENĂCHESCU, S. STĂNESCU, *Contributions à l'étude des critères biologiques d'âge*. Dans « Hommage à C. I. Parhon », Ed. Academiei, Bucarest, 1966, 493—504.
27. A. ASLAN, AL. VRĂBIESCU, V. BUŞILĂ, *Aspects du réglage de l'appareil cardiovasculaire chez les âgés*, Fiziol. norm. patol., **14,** *6*, 1968, 561—565.

ROMANIAN J. GERONT. GERIATRICS, 1981, 2, 1, p. 25–35

EVALUATION OF THE EFFECT OF ASLAVITAL AND GEROVITAL H_3 THERAPY ON ERYTHROPOIESIS BY THE RETICULOCYTE PRODUCTION INDEX

ANA ASLAN, ELEONORA VASILIU, RODICA PETOLEA, THEODORA IONESCU

The National Institute of Gerontology and Geriatrics, Bucharest, Romania

ANGELICA ALBU, SPERANȚA HALUNGA-MARINESCU

"N. Gh. Lupu" Institute of Internal Medicine

Summary. Erythropoietic functionality was investigated by means of the reticulocyte production index (RPI) on a group of 40 subjects with no erythrocytary pathologic manifestations, belonging to the sample undergoing eutrophic treatment in the long-stay unit of the National Institute of Gerontology and Geriatrics. These were compared to a group of untreated controls and to a group of 10 patients displaying various types of anaemias.

In the group subjected to the eutrophic treatment according to Prof. Dr. Ana Aslan's method, reticulocyte production index was normal in 35% of the cases, low in 17.5% and high in 47.5%, as compared to the control group, in which it displayed an obvious decreasing tendency (it was normal in 22.5% and low in 77.5% of the cases), pointing to the erythropoiesis depression processes in the elderly.

Considering the conclusive results concerning the erythron functionality obtained by a simple technique which also permits the gentle handling of the investigated subject, this method, applied for the first time in the elderly in Romania, is recommended as a routine test, a practical and objective criterion for the evaluation of the dynamics of the positive effects induced by Gerovital H_3 and Aslavital eutrophic treatment on erythropoiesis.

One of the most important tests for the evaluation of the erythropoietic functional capacity, is the reticulocyte count in peripheral blood, which is at the same time easy to apply on the subject under investigation.

As known, the reticulocyte is a young red cell that retains from the erythroblast a few organelles (mitochondria, polyribosomes and various ribonucleic acids), demonstrable with brilliant cresyl blue precipitation as a granular or filamentous network, which tends to reduce as the cell matures.

Reticulocyte count in peripheral blood reflects the medullary erythropoietic activity. The common methods for reticulocyte count express the reticulocyte number in relative, percent values, so that evaluation is arbitrary. Absolute count, which is the most advisable, involves additional apparatus that makes it difficult to apply on a large scale.

Hillman and Finch [1], quoted for the first time in Romanian literature by Grigoriu [2], correlated the results of percent count with the hematocrit and life span of reticulocytes and obtained a more complex image of the erythropoietic activity by means of the reticulocyte production index.

This method yields conclusive results on the erythron functionality using a simple technique, which also permits the gentle handling of the investigated subject.

As the eutrophic therapy based on Prof. Dr. Aslan's method [3—7] is a long-term therapy, the calculation of the reticulocyte production index (RPI) might become a practical hematologic criterion for the evaluation of the dynamics of the effects induced by Gerovital H_3 and Aslavital on erythropoiesis.

As the geriatric treatment method requires periodical hematological investigations [8], which must be easy to apply, well tolerated by the elderly and yet provide the best results, RPI exactly meets these necessities.

MATERIAL AND METHOD

Erythropoietic regenerative capacity was investigated on a group of 40 subjects belonging to the sample undergoing eutrophic treatment in the long-stay unit of the National Institute of Gerontology and Geriatrics.

The subjects, aged 75—95, were subjected to Gerovital H_3 or Aslavital treatment, for long periods ranging from 2 to 15 years, in series of 12 injections over 4 weeks, followed by 24-day breaks. The erythropoietic activity of these subjects was investigated by RPI after a period of 6 months without eutrophic treatment.

We should mention that neither of these subjects displayed clinical or paraclinical manifestations of anaemic syndrome (Tables 1 and 2).

Table 1

Percentage of reticulocytes and the reticulocyte production index in the subjects of the Gerovital H_3-treated sample

Name	Age	Sex	Reticulocytes %	RPI
P.E.	86	F	0.7	1.08
H.V.	95	M	2.0	1.52
N.T.	80	F	4.0	1.06
D.E.	79	F	1.2	0.77
D.I.	75	M	1.6	1.49
G.C.	87	F	0.6	0.93
P.M.	74	F	1.8	1.85
N.M.	80	F	1.8	1.17
P.A.	81	F	1.4	1.86
D.L.	79	F	1.6	1.30
T.A.	88	F	1.7	1.00
S.C.	88	F	1.7	1.66
B.R.	77	M	1.4	1.06
N.A.	85	M	1.5	1.36
C.S.	95	M	1.6	1.90
R.S.	82	M	1.6	1.49
R.F.	74	F	1.5	1.50
U.E.	79	F	1.7	1.62
O.D.	93	F	1.5	1.60
P.J.	88	F	0.8	1.30
E.E.	75	F	1.5	1.21
B.V.	82	F	1.3	1.12
I.F.	88	F	0.8	0.80
N.D.	80	M	0.7	0.67

Table 2

Percentage of reticulocytes and the reticulocyte production index in the subjects of the Aslavital-treated sample

Name	Age	Sex	Reticulocytes %	RPI
S.R.	82	F	0.7	1.25
G.M.	85	F	0.9	1.40
C.T.	89	M	0.7	0.97
A.A.	73	F	0.9	0.77
C.V.	71	M	1.5	1.53
P.D.	74	F	1.4	0.98
C.A.	93	M	1.1	0.80
S.N.	82	M	0.9	0.85
V.E.	84	F	1.3	0.80
S.M.	79	F	1.8	1.40
N.E.	85	F	1.6	1.12
L.M.	87	F	1.8	1.80
L.F.	88	F	1.4	0.95
A.I.	84	M	0.9	0.85
C.V.	88	M	0.8	0.78
B.E.	84	M	0.9	0.85

The erythropoietic regenerative capacity was also investigated on a group of 40 subjects aged 55—95, without anaemic syndromes, who had never been submitted to eutrophic treatment (Table 3).

Table 3

Percentage of reticulocytes and the reticulocyte production index in the control subjects

Name	Age	Reticulocytes %	RPI
1	2	3	4
M.M.	73	0.7	0.63
I.R.	81	0.7	0.90
B.N.	58	0.7	0.80
V.S.	68	0.7	0.37
M.I.	62	0.8	0.90
V.P.	71	0.9	0.66
C.A.	82	0.9	0.51
V.A.	85	0.8	0.95
P.E.	73	0.6	0.64
C.R.	78	0.8	0.93
G.M.	76	0.6	0.62
T.E.	70	0.9	0.61
K.C.	74	0.9	1.20
M.E.	77	0.8	0.80
B.E.	74	1.7	0.59
M.C.	65	0.5	0.41
T.R.	60	0.7	0.50
S.E.	79	1.2	0.50
B.L.	62	0.7	0.76
B.C.	58	0.5	0.46
S.P.	71	0.5	0.74

Table 3 (continued)

1	2	3	4
N.N.	84	0.7	0.51
S.I.	74	0.7	0.38
D.Z.	81	0.5	0.43
C.C.	74	0.4	0.70
G.P.	71	0.9	0.74
C.A.	56	0.8	0.69
H.C.	91	0.9	0.58
C.O.	73	0.9	0.76
B.N.	83	1.0	0.97
H.G.	74	1.2	0.92
G.I.	72	0.8	0.72
P.E.	70	0.9	0.57
A.A.	59	1.1	0.91
G.M.	70	0.9	0.76
J.A.	62	1.0	0.97
J.I.	65	0.9	0.61
I.I.	78	0.7	0.68
I.R.	77	0.7	0.46
C.V.	82	0.6	0.58

In order to point out the clinical value of RPI, 10 patients who displayed different types of anaemias (Tables 4 and 5) were also followed up in this test, illustrating the possibility to define more accurately the regenerative or non-regenerative character of erythropoiesis.

Table 4

Percentage of reticulocytes and the reticulocyte production index prior and after treatment in regenerative anaemias

Patient's name	Hematocrit (%)		R %/RPI		Diagnosis
	prior to treatment	after treatment	prior to treatment	after treatment	
N.T.	24	34	4/1.05	9/4.5	anaemia due to duodenal ulcer with melena
N.A.	26	36	0.6/0.1	1.8/0.9	hypochromic iron-deficiency anaemia
S.S.	30	50	2.6/0.8	1.8/1.7	iron-deficiency anaemia
R.V.	27	30	1.2/0.5	2.5/1.3	sidero-blastic anaemia
B.L.	32	40	1.4/0.8	3.2/2.8	metrorrhagias, secondary anaemia

As RPI allows an appropriate evaluation of erythrocyte life span, this aspect was considered on a sample of 14 subjects from the Institute of Internal Medicine, at the same time with the assessment of erythrocyte life span by means of the isotopic method with radioactive chromium (Table 6).

Table 5

Percentage of reticulocytes and the reticulocyte production index prior to and after treatment in non-regenerative anaemias

Patient's name	R %/RPI		Hematocrit (%)		Diagnosis
	prior to treatment	after treatment	prior to treatment	after treatment	
C.I.	2.9/0.4	0.4/0.04	18	34	myeloproliferative syndrome
I.I.	2.8/1.2	1/0.4	30	39	Hodgkin's disease
I.N.	1.5/1	6/0.5	10	14.5	chronic lymphatic leukosis
M.V.	1.2/0.2	0.1/0.05	16	36	acute leukaemia
C.D.	0.7/0.2	0.1/0.04	28	34	chronic myeloid leukosis

Table 6

Life span of the erythrocyte calculated by the reticulocyte production index as compared to the isotopic method with radioactive chromium

Patient's name	Life span in RPI	Life span with isotopes
1	2	3
M.I.	↓	↓
S.F.	↓	↓
P.D.	↓	↓
B.M.	↓	↓
G.M.M.	↓	↓
M.S.	↓	↓
L.T.	↓	↓
N.A.	↓	N
P.L.	↓	↓
P.E.	↓	↓
P.L.	↓	N
C.M.	↓	↓

Table 6 (continued)

1	2	3
N.R.	↓	↓
S.C.	↓	↓
	total patient's concordance	12
	total patient's non-concordance	2 n = normal ↓ = low

Statistical analysis. The results were expressed as arithmetical mean of N values. Standard errors were calculated and standard errors of the mean (SEM) were used to indicate the statistical significance of the results.

RESULTS AND DISCUSSION

After a 3—4-day maturation, reticulocytes pass from the hematopoietic marrow into the peripheral blood, where they change into red cells after 24 hours, the maturation time varying in relation to the hematocrit.

In their researches of 1969, Hillman and Finch [1] induced different degrees of anaemia by repeated phlebotomies in hematologically normal persons, and demonstrated the premature release of reticulocytes from the bone marrow as well as the prolongation of the survival time of circulating reticulocytes proportional to anaemia severeness. Thus, while in a person with a hematocrit of 45% the reticulocytes stay in the peripheral blood for one day, in an anaemia-afflicted one with a hematocrit under 20% they stay two days and a half (Table 7).

Table 7

Maturation time of reticulocytes in relation to the hematocrit

Hematocrit (%)	Maturation time (days)	
	Hemato-poietic marrow	Peripheral blood
45	1.5	1.0
35	1.0	1.5
25	0.5	2.0
15	0.0	2.5

The variations in the maturation time of medullary reticulocyte in relation to the hematocrit are represented in Fig. 1.

In the marrow, the normal maturation time of reticulocytes reduces to one day and a half, for a very small hematocrit.

Reticulocyte count becomes thus an important indicator of the marrow capacity to produce erythrocytes, reflecting therefore the erythropoietic function.

The common technique used to express the reticulocyte number in percent takes into account neither the total number of red cells in the peripheral blood nor the maturation time of reticulocytes.

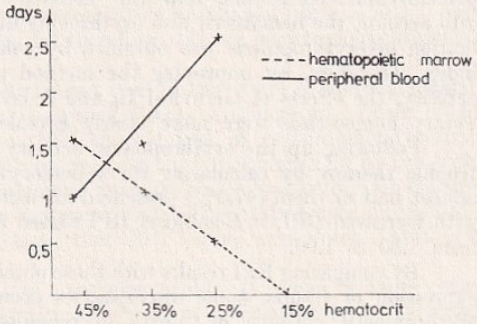


Fig. 1. — Variations of reticulocyte maturation time in the peripheral blood and hematopoietic marrow in relation to hematocrit.

Applying a correction to the percentage index in relation to these factors we get a more objective evaluation. Thus, a first correction is obtained in relation to the hematocrit. For example: for a reticulocyte number of 9% and a hematocrit of 20%, the corrected number is $9 \times \frac{20}{45} = 4\%$.

But taking into consideration the variations in the survival time in relation to the hematocrit, a new correction is required in relation to the maturation time of reticulocytes in the peripheral blood, using the following formula [9] [10]:

$$\frac{\text{Corrected number of reticulocytes}}{\text{maturation time}} = \text{reticulocyte production index}$$

This index is usually 1. The concomitant application of the 1st and 2nd correction leads to the following formula:

$$\text{Reticulocyte number } \% \times \frac{\frac{\text{hematocrit found}}{45}}{\text{maturation time}} = \text{RPI}$$

For example: $R\% = 4\%$ $\quad \text{RPI} = \frac{4}{2.25} = 1.8$

It is important to calculate RPI as it can be used in the orientative evaluation of erythrocyte life span without using the method with radioactive isotopes, due to a perfect equilibrium between production and destruction of erythrocytes in a constant hematocrit.

RPI calculation, a recent technique which has not been used yet in routine practice, is characterized by simplicity and enables longitudinal studies on the elderly in the geriatric treatment. As the eutrophic treatment according to Prof. Dr. Ana Aslan's method is a long-term treatment [11], our research continues.

The Gerovital H_3- and Aslavital-treated sample of elderly patients was under permanent clinical and paraclinical observation. The periodical investigations did not point out changes directly or indirectly involving erythropoiesis, as none of the subjects displayed anaemia symptoms.

Concomitantly with current hematological investigations, the eutrophic therapy effect on the erythron functionality was observed in its dynamics. Therefore, the reticulocyte count was performed according to the classical method with percent-expressed results, and the necessary corrections were applied taking into account the hematocrit and erythrocyte life span. Thus, a more objective evaluation of erythropoiesis was obtained by calculating the reticulocyte production index. Therefore, by improving the method used to evidence the erythropoietic activity, the effects of Gerovital H_3 and Aslavital on the maintenance of erythrocytary homeostasis were more clearly revealed.

Following up the erythropoietic activity of 40 elderly subjected to the eutrophic therapy by calculating the reticulocyte production index, we found that almost half of them (47.5%) presented an increased RPI, namely: of the 19 cases with increased RPI, in 9 subjects RPI varied from 1.21 to 1.50, and in 10 subjects from 1.50 to 1.90.

By comparing RPI results with those obtained by the method using the percent expression of results, some discrepancies occur which require a research on the erythropoietic activity by means of reticulocythemia, taking into account the hematocrit and reticulocyte life span, factors on which RPI calculation is based.

Thus, in almost half of the cases (9 of 19) an increased RPI was observed, while no change was recorded when using the method with percent-expressed results. Illustrative in this respect is the subject P.A. with 14% reticulocytes in the first evaluation but with RPI 1.87, that is, almost double the normal, as a result of corrections, or the subject S.R. with a tendency to erythropoietic hypoplasia revealed by the percent calculus (0,7% reticulocytes) but with a slightly increased index, of 1.25.

In 35% of the subjects undergoing eutrophic therapy no changes in erythropoietic homeostasis could be noticed. For the rest of 17.5% of the treated elderly, erythropoiesis developed similarly to most of the untreated aged subjects, therefore with different degrees of hyporegenerative manifestations (Table 8).

Table 8

Evaluation of the reticulocyte production index in the samples submitted to eutrophic therapy as against the controls

RPI	
Control sample (%)	Sample submitted to eutrophic treatment (%)
	47.5 ↑
22.5 n	35 n
77.5 ↓	17.5 ↓

In the sample of 40 untreated control elderly, calculation of RPI pointed out in 31 subjects (77.5%), the hyporegenerative erythropoietic aspect, well-known with the elderly [12], while 9 subjects (22.5%) displayed no variations from this point of view.

Comparing the reticulocyte number (the common method) with RPI, we can notice (Tables 1—3) that the values of the latter are much lower than those expressed in percent, the data found in relation to the hematocrit and reticulocyte life span reflecting more faithfully the diminution of the erythropoietic activity with age.

In order to control the clinical value of RPI, it was also calculated in a group of 10 patients with anaemic syndrome, hospitalized in the "N. Gh. Lupu" Institute of Internal Medicine.

We could distinguish: 5 cases of regenerative anaemias (Table 4) and 5 cases of non-regenerative anaemias (Table 5), therefore with an increased erythropoietic activity.

The analysis of these cases pointed out that in the group of non-regenerative anaemias of leukosis, especially in Hodgkin's disease, although as a result of the treatment the hematocrit increased, RPI showed lack of erythropoietic activity at the marrow level. Total non-reactivity was obviously accounted for by the evolution of the underlying disease. Hematocrit increase was apparent due to repeated transfusion within the substitution treatment. Comparing reticulocyte number (the common method) with RPI, we noticed that RPI values were lower, pointing to an actual lack of regeneration.

RPI calculation in regenerative anaemias (Table 4) allows a more exact evaluation of the therapeutic effect than the percent calculation of reticulocytes. For example, after the treatment patient N. T. displayed a twofold percent number of reticulocytes, whereas RPI was 4 times higher, which points out the actual reactive capacity of the erythropoietic marrow.

The determination of the erythrocyte life span by means of radioactive chromium method as well as by RPI calculation was concordant in 12 of 14 analysed cases displaying anaemic syndrome. The index importance is thus evident also for the orientative evaluation of the circulating erythrocyte life span (Table 6).

The statistical analysis pointed out different values, significantly increased in the samples subjected to eutrophic therapy: 1.5—1.6 as compared to 0.7 for the percent reticulocyte number and 2.61—1.06 as compared to 0.66 for the reticulocyte production index $p < 0.002$ (Table 9).

Table 9

Average values of reticulocytes and the reticulocyte production index in the subjects submitted to eutrophic therapy as against the controls

Subjects	No. of cases	Mean age	Mean R %	Mean RPI
Gerovital-treated	24	83	1.5	2.61
Aslavital-treated	16	83	1.6	1.06
Controls	40	72	0.7	0.66

The above mentioned data show that this technique evaluating the erythron activity by the reticulocyte production, is indispensable to current investigation in the longitudinal studies on the elderly.

Being a simple and easy reproducible method it is used in following up the dynamics of the effects of Gerovital H_3 and Aslavital eutrophic therapy in the geriatric treatment based on Prof. Dr. Aslan's method.

CONCLUSIONS

1. For the first time in Romania RPI was investigated on a sample of 80 elderly subjects (55—95 years old), of which 40 belonged to the sample undergoing eutrophic therapy in the long-stay unit of the National Institute of Gerontology and Geriatrics and 40 were untreated controls.

2. In the sample subjected to the eutrophic treatment based on Prof. Dr. Ana Aslan's method, the reticulocyte production index was normal in 35% of the cases, low in 17.5% and increased in 47.5% as compared to the control sample in which an obvious decreasing tendency was noticed (RPI was normal in 22.5% and low in 77.5% of the cases), pointing to the erythropoiesis depression processes in the elderly.

3. Since RPI calculation provides a correct reading of the erythrocyte production/destruction ratio, and is more available as compared to other investigation methods of the erythropoietic function, especially in the elderly, this test is recommended to be used in current practice to follow up the efficiency of the eutrophic therapy with Gerovital H_3 and Aslavital.

Résumé. On a étudié le fonctionnement érythropoiétique par l'indice de production des réticulocytes (IPR) chez un groupe de 40 sujets sans manifestations pathologiques érythrocytaires, qui font partie du lot soumis au traitement biotrophique au foyer de l'Institut national de gérontologie et gériatrie, par rapport à un lot de 10 malades à différents types d'anémies.

Chez le lot de patients soumis au traitement eutrophique selon la méthode Aslan, l'indice de production des réticulocytes a été normal dans 35% des cas, diminué dans 17,5% et accru dans 47,5%, par rapport au lot temoin, où il a présenté une évidente tendance de diminution (il a été normal dans 22,5% et diminué dans 77,5% des cas), indiquant les processus de dépression de l'érythropoïèse chez les sujets âgés.

Cette méthode, appliquée pour la première fois en Roumanie dans le traitement des personnes âgées, est recommandée comme un test de routine étant donné qu'elle permet d'obtenir des résultats concluants concernant le fonctionnement de l'érythrone par l'intermédiaire d'une technique simple qui a aussi l'avantage de ménager au maximum le sujet investigué.

REFERENCES

1. R. S. HILLMANN, A. C. FINCH, *The misused reticulocyte*. Brit. J. Haemat., **17**, 1969, 313—317.
2. G. M. GRIGORIU, *Reticulocyte count in clinical practice*. Doc. Haemat., **2**, 1971, 73—78.
3. A. ASLAN, C. DAVID, S. CÎMPEANU, *Metabolic effects of procaïne therapy* (in Romanian). Fiziol. norm. patol. (Bucharest), **79**, 1963, 321—331.
4. AL. VRĂBIESCU, *Effets physiologiques et pharmacologiques de la procaïne H_3 (Gérovital)*. Bull. Soc. Méd. Paris, **166**, 7, 1965, 7.
5. A. ASLAN, *Bases théoriques de la thérapie à la procaïne dans la prévention de la sénescence*. In: *Aslavital*, Bucharest, 1975, p. 12—26.
6. A. TEITEL, C. MARCU, A. POPA, *Sur l'action métabolique de la procaïne*. Conf. Naț. Fiziol., mai 1960, Bucharest.

7. A. ASLAN, AL. VRĂBIESCU, C. DOMILESCU, L. CÎMPEANU, M. COSTINIU, S. STĂNESCU, *Long-term treatment with procain (Gerovital H_3) in Albino rats*. J. Geront., **20**, *1*, 1965.
8. A. ASLAN, G. ENĂCHESCU, *Etude thérapeutique sur l'Aslavital. VI. Données hématologiques*. In: *Aslavital*, Bucharest, 1975, p. 99—110.
9. ȘT. BERCEANU et al., *Clinical Hematology* (in Romanian). Ed. medicală, Bucharest, 1977, p. 919.
10. E. BUTOIANU, ȘT. NICOARĂ, *Hematological Vademecum* (in Romanian). Ed. medicală, Bucharest, 1973, p. 33.
11. A. ASLAN, C. DAVID, AL. VRĂBIESCU, *Etude thérapeutique longitudinale sur l'Aslavital*. In: *Aslavital*, Bucharest, 1975, p. 40—42.
12. M. S. HTOO, R. L. KOFKOFF, M. L. FREEDMAN, *Erythrocyte parameters in the elderly; an argument against new geriatric normal values*. J. amer. Geriat. Soc., **XXVII**, *12*, 1979, 547—551.

ROMANIAN J. GERONT. GERIATRICS, 1981, 2, 1, p. 37–47

CONTRIBUTIONS TO THE EPIDEMIOLOGICAL STUDY OF CARDIOVASCULAR PATHOLOGY IN THE AGED

M. DUMITRU, GH. GHENCIU, SILVIA GALAFTION

The National Institute of Gerontology and Geriatrics, Bucharest, Romania

Summary. The paper presents some statistical-epidemiological data of a study on the structure of morbidity by general pathology and particularly by cardiovascular diseases in the aged hospitalized in a specialized unit — The National Institute of Gerontology and Geriatrics.

Statistical techniques were used.

The major reasons for the hospitalization of the elderly and aged patients were the diseases of the circulatory apparatus (42.0%) followed by illnesses of the osteoarticular system (19.7%).

The analysis of the pathological loading by relating the overall number of diseases to persons aged 60 and more, pointed out a number of 351.7 diseases per 100 hospitalized persons. The heaviest pathological loading was found in persons aged 80 and more. The highest prevalence was pointed out in cardiovascular diseases, particularly in the age-decades 70—79, and 80 and more.

The analysis of the cardiovascular pathology in hospitalized aged persons with arterial hypertension (AHT) pointed out the highest prevalence in the age-decade 70—79: 176.2 cardiovascular diseases per 100 patients with AHT. The pathological loading was much lower in women with AHT: 117.2 cardiovascular diseases per 100 hospitalized patients as against 149.0 in men.

Among the clinical forms of AHT, essential hypertension had the highest prevalence in patients aged 60—69 and 70—79.

Systolic AHT ranged first in patients aged 80 and more.

At present, cardiovascular diseases are the first cause of morbidity and mortality with the aged [1]. Based on epidemiological studies, the experts of the World Health Organization [2] elaborated and experimented primary methods to prevent the various clinical forms of ischemic cardiopathy, the vascular disease with the highest mortality rate.

One of the most certain correlations is that established between the prevalence of deaths through cardiovascular diseases within overall deaths and the mortality rates through these diseases on the one hand, and demographic aging rate on the other.

In Romania, in 1979, deaths through cardiovascular diseases represented 50.6% of overall deaths in urban areas and 56.5% of overall deaths in rural areas.

The indices of specific mortality through cardiovascular diseases were 4.0‰ in urban areas and 6.56‰ in rural areas.

During the same year, the indices of demographic aging (prevalence of the population aged 60 and more within the overall population) were lower in urban (10.4%) as compared to rural (15.7%) areas.

The present study aims at pointing out the structure of the pathology in the National Institute of Gerontology and Geriatrics (NIGG), which is specialized in providing medical care for the aged population.

MATERIAL AND METHOD

The study was conducted on 2,166 elderly and aged patients hospitalized and treated in the NIGG over the period 1977—1978 (1,372 women and 794 men). 1,022 patients (714 women and 308 men) were under treatment for various cardiovascular diseases.

516 patients (354 women and 162 men) hospitalized for various clinical forms of AHT were also included in the study.

The main methods used to reach the aim of the present study were statistical; among them mention should be made of:

— the method of statistical classification;

— the method of indices (the degree of pathological loading expressed by the number of diseases per 100 hospitalized patients and structural indices);

— the graphical method.

RESULTS AND COMMENT

THE DEGREE OF PATHOLOGICAL LOADING IN ELDERLY AND AGED PATIENTS HOSPITALIZED IN THE NIGG OVER THE PERIOD 1977—1978

The pathology of the 2,166 hospitalized patients on admittance was included in the following 12 classes of diseases:

1. — Infectious and parasitic diseases
2. — New growths
3. — Endocrine and metabolic diseases
4. — Blood and hematopoietic diseases
5. — Mental disorders
6. — Diseases of the central nervous system (DCNS)
7. — Diseases of the circulatory apparatus
8. — Diseases of the respiratory apparatus
9. — Diseases of the digestive apparatus
10. — Uro-genital diseases
11. — Diseases of the skin
12. — Diseases of the osteoarticular system.

The degree of pathological loading was calculated by the relation between the overall number of diseases and the number of patients aged 60 and more, hospitalized in the NIGG; the result was multiplied by 100. The calculation was made by group of diseases, age and sex.

The analysis of the data pointed out (Fig. 1):

a) 351.7 diseases were discovered per 100 hospitalized patients, the number being lower (343.4) in the first age-decade analysed (60—69) and almost constant in the next 2 age-decades (356.5 in patients aged 70—79 and 356.3 in patients aged 80 and more).

The distribution by sex pointed out lower figures in men (347.2 diseases per 100 men as against 352.5 diseases per 100 women).

The distribution by age-decade revealed the number of diseases per 100 men to be 340.6 in the decade 60—69, 348.2 in the decade 70—79 and 356.3 in the decade 80 and more, the latter decade having the heaviest pathological loading.

The number of diseases per 100 women was 340.5 in the decade 60—69, 361.1 in the decade 70—79 and 356.3 in the decade 80 and over.

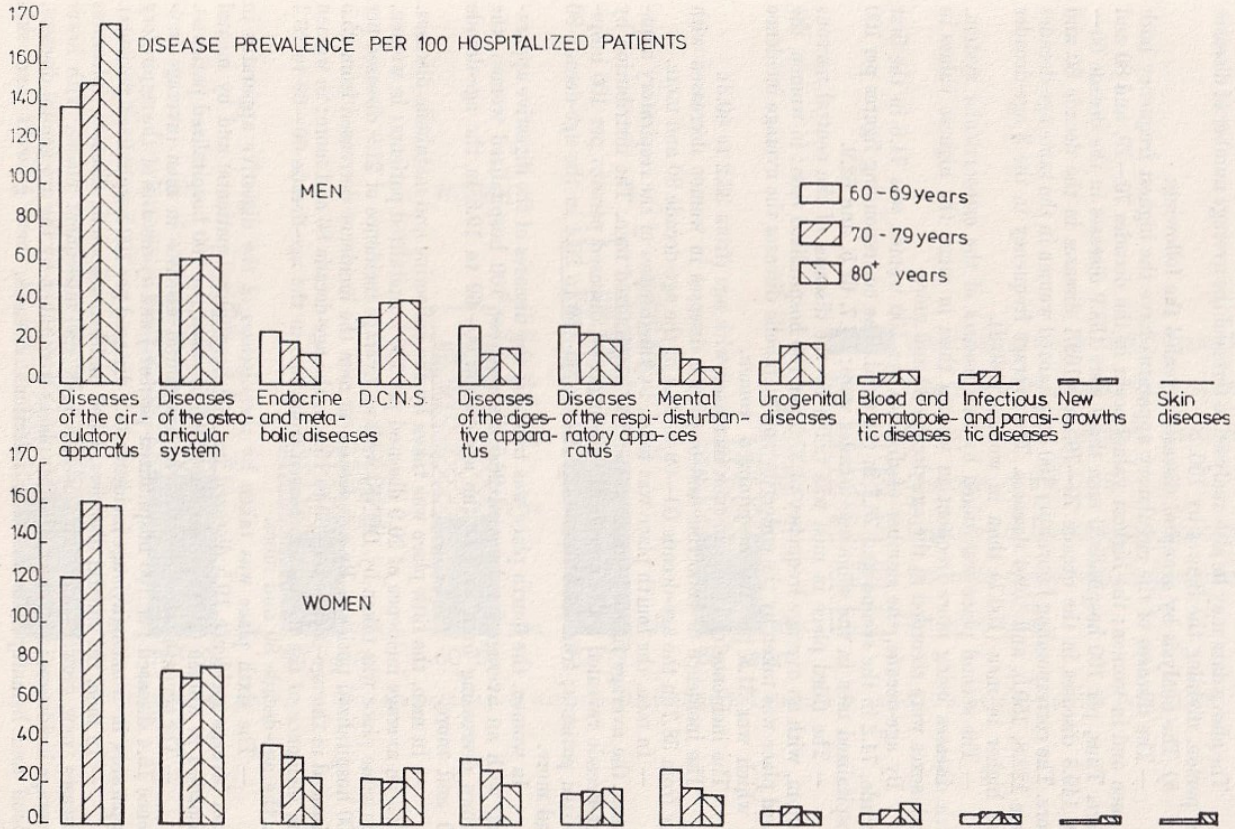


Fig. 1. — Degree of pathological loading in the patients aged 60+, hospitalized in the NIGG over the period 1977—1978.

The above data may be also analysed in terms of the average number of diseases per person, dividing the figures by 100.

b) The analysis by group of diseases revealed the following:

— The diseases of the circulatory apparatus have the highest frequency both in men and in women; the highest values occur in the decades 70—79, and 80 and more. Thus, per 100 hospitalized men there were 138.9 diseases in the decade 60—69, 149.8 diseases in the decade 70—79, and 169.1 diseases in the decade 80 and more. The corresponding figures per 100 hospitalized women in the same age-decades were 122.8, 159.5, and 159.4 diseases. The average frequency in the 3 age-decades was higher in men (150.1) than in women (146.2).

— The second place was taken by the diseases of the osteoarticular system, such diseases being more frequent in women than in men; the highest values in both sexes were recorded in the age-decade 80 and more.

By age-decade, the number of diseases per 100 women was 74.6 in the first decade, 74.2 in the second and 76.7 in the third. The corresponding figures per 100 hospitalized men in the same age-decades were: 54.7, 62.5, and 62.9.

— The third place in men was taken by the diseases of the central nervous system, with an average frequency of 37.5 per 100 hospitalized men; in women, the third place was taken by the endocrine and metabolic diseases the average incidence of which was 31.8 per 100 hospitalized women.

The incidence of DCNS in men increased with age (from 33.2 to 40.3).

The incidence of endocrine and metabolic diseases in women decreased with age from 38.7 in the age-decade 60—69 to 20.4 in the age-decade 80 and more.

— In men, the fourth place was taken by the diseases of the respiratory apparatus, the average figure being 23.3 per 100 hospitalized men. The distribution by age-decade revealed a decrease in the incidence of diseased persons per 100 hospitalized patients; from 26.5 in the age-decade 60—69 to 20.4 in the age-decade 80 and more.

In women, the fourth place was taken by the diseases of the digestive apparatus, with an average incidence of 26.5 diseased per 100 hospitalized women, the values decreasing from 31.4 in the age-decade 60—69 to 19.8 in the age-decade 80 and more.

— In men, the fifth place was taken by the endocrine and metabolic diseases, with an average incidence of 20.9 diseased per 100 hospitalized patients; in women, the same place was taken by DCNS, with an average incidence of 21.9 diseased per 100 hospitalized patients. By age-decade, in men the incidence decreased from 25.5 diseased in the age-decade 60—69 to 13.3 in the age-decade 80 and more; in women the incidence of the diseases increased from 20.8 in the age-decade 60—69 to 26.4 in the age-decade 80 and more.

— The sixth place was taken by the diseases of the digestive apparatus in men (averge incidence 19.5 diseased per 100 hospitalized patients) and by mental disorders in women (average incidence 19.6 diseased per 100 hospitalized patients).

— The seventh place was taken by uro-genital diseases in men (average incidence 15.4 diseased per 100 hospitalized patients) and by diseases of the respiratory apparatus in women (average incidence 14.4 diseased per 100 hospitalized patients).

— In men, the mental disorders, blood and hematopoietic diseases, infectious diseases, new growths and skin diseases took the subsequent places, with lower average incidences; in women, the last places were taken by the uro-genital diseases, blood and hematopoietic diseases, infectious diseases, new growths and skin diseases.

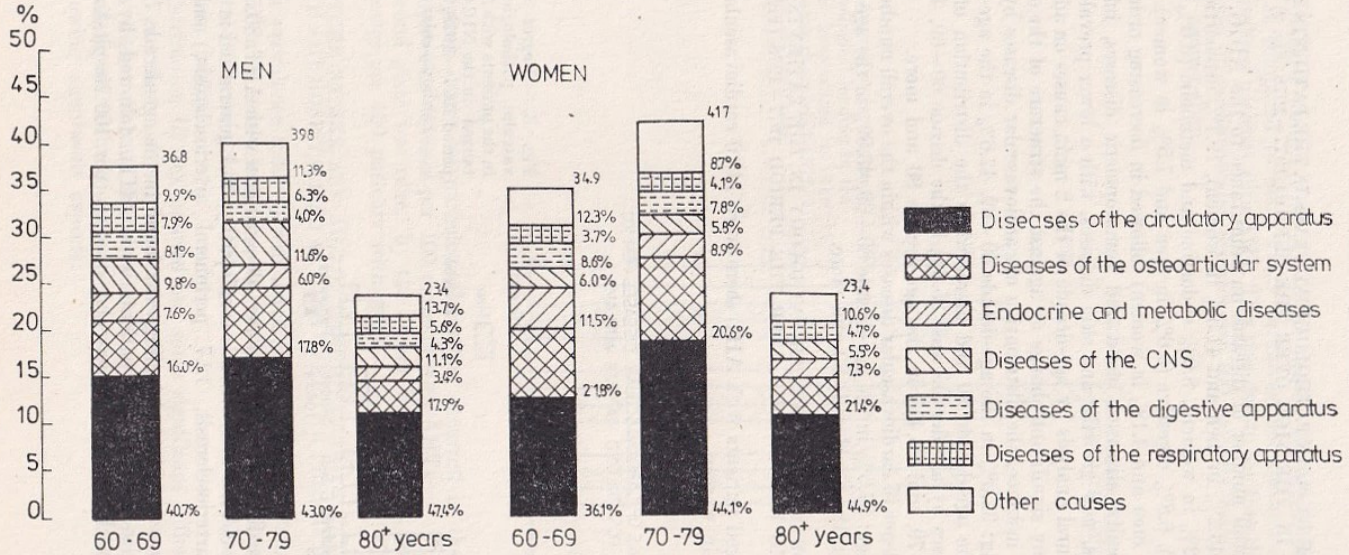


Fig. 2. — Structure by sex and age of the main pathological classes in the patients hospitalized in the NIGG over the period 1977—1978.

THE STRUCTURE BY MAIN PATHOLOGICAL CLASS IN THE PATIENTS HOSPITALIZED IN THE NIGG OVER THE PERIOD 1977—1978 (Fig. 2)

Of the overall number of diseases on admittance to the NIGG, 42.0% were cardiovascular (43.2% in men and 41.5% in women), 19.7% osteoarticular (17.2% in men and 21.2% in women), 8.0% endocrine and metabolic (6.0% in men and 7.0% in women), 6.8% digestive (5.6% in men and 7.5% in women), 5.2% respiratory (6.7% in men and 4.1% in women) followed in decreasing order by mental disorders, uro-genital diseases, blood and hematopoietic diseases, infectious and parasitic diseases, new growths and skin diseases, with a lower prevalence.

The structural analysis by age-decade of the 2 main causes on admittance did not point out any significant change as against the structure of the overall group of subjects. For instance, the distribution of cardiovascular diseases by age-decade was the following: 32.0% in the age-decade 60—69, 42.6% in the age-decade 70—79, 25.4% in the age-decade 80 and more, while the distribution of the overall number of diseases by age-decade was: 35.8% in the decade 60—69, 40.8% in the age-decade 70—79, and 23.4% in the age-decade 80 and more.

The prevalence of cardiovascular diseases within the overall number of diseases increased with age: 37.5% in the age-decade 60—69, 43.8% in the age-decade 70—79, and 45.7% in the age-decade 80 and more.

PREVALENCE OF CARDIOVASCULAR PATHOLOGY IN THE PATIENTS WITH AHT HOSPITALIZED IN THE NIGG OVER THE PERIOD 1977—1978 (Figs 3 and 4)

Per 100 aged patients with AHT there were 149.0 cardiovascular diseases in men and 117.2 in women.

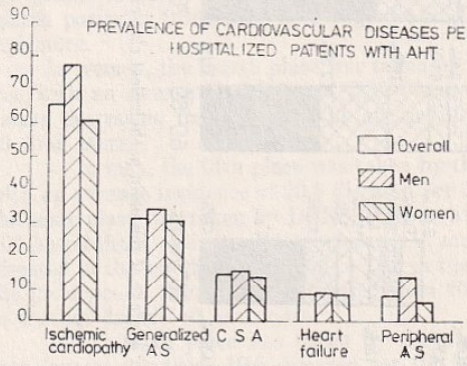


Fig. 3. — Degree of cardiovascular pathological loading in the patients with AHT hospitalized in the NIGG over the period 1977—1978, by sex and cardiovascular disease.

Of 149.0 cardiovascular diseases per 100 aged men with AHT, 80.5 represented coronary arteriosclerosis and ischemic cardiopathy, 33.1 generalized arteriosclerosis, 14.9 cerebral arteriosclerosis, 12.7 peripheral arteriosclerosis, and 7.8 heart failure.

The heaviest pathological loading was found in the age-decade 70—79 (176.2 cardiovascular diseases per 100 patients with AHT), followed by the decade 80 and more, with 166.7 cardiovascular diseases per 100 hospitalized patients with AHT.

In hospitalized women with AHT, the degree of pathological loading was much lower as compared to men: 117.2 cardiovascular diseases as against 49.0 per 100 hospitalized patients with AHT. This was due to the fact that the incidence of all categories of cardiovascular diseases per 100 patients with AHT was lower in women as against men.

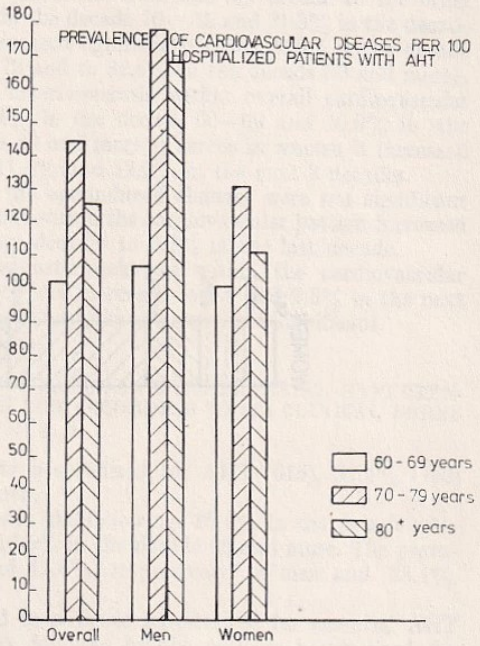


Fig. 4. Degree of cardiovascular pathological loading in the patients hospitalized in the NIGG over the period 1977—1978, by sex and age.

The highest degree of pathological loading occurred in the decade 70—79 (130.0 cardiovascular diseases per 100 patients with AHT).

The second place was taken by the decade 80 and more, with 109.7 cardiovascular diseases per 100 patients with AHT.

THE STRUCTURE BY SEX AND AGE OF CARDIOVASCULAR PATHOLOGY IN PATIENTS WITH AHT HOSPITALIZED AT NIGG OVER THE PERIOD 1977—1978 (Fig. 5)

A high prevalence (53.9%) was noted in patients hospitalized for coronary arteriosclerosis and ischemic cardiopathy followed by generalized arteriosclerosis (24.1%), cerebral arteriosclerosis (10.6%), heart failure (5.9%), and peripheral arteriosclerosis (5.5%).

The distribution by sex pointed out some significant differences:

— The prevalence of peripheral arteriosclerosis within overall cardiovascular diseases was higher in men (8.5%) than in women (3.8%).

The analysis of the variations in the prevalence by cause and age-decade pointed out the following significant aspects:

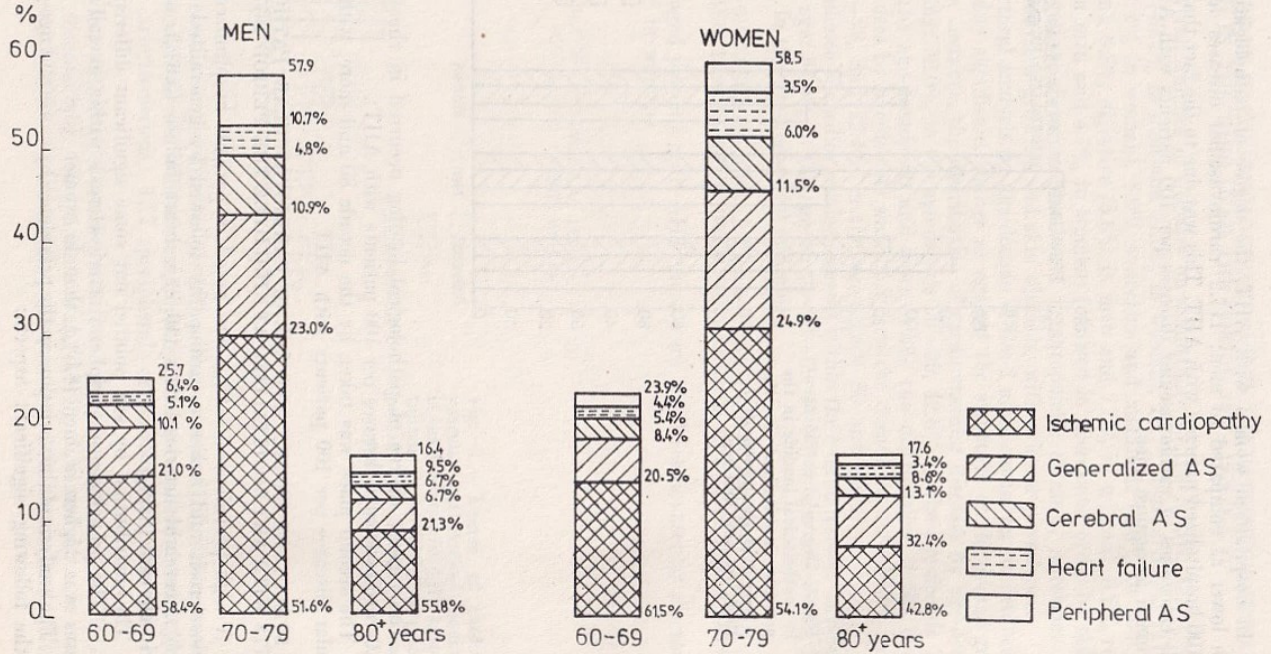


Fig. 5.—Structure by sex and age of cardiovascular pathology in the patients with AHT hospitalized in the NIGG over the period 1977—1978

— The prevalence of coronary arteriosclerosis and ischemic cardiopathy within the overal cardiovascular diseases in men did not show a clear-cut tendency from one age-decade to the other, whereas in women it decreased from 61.5% in the decade 60—69 to 54.1% in the decade 70—79 and to 42.8% in the decade 80 and more;

— The prevalence of generalized arteriosclerosis within overall cardiovascular diseases in men did not show large variations from one age-decade to the other (21.2% in the decade 60—69, 22.9% in the decade 70—79, and 21.3% in the decade 80 and more), whereas in women it increased significantly (from 20.5% in the decade 60—69 to 24.7% in the decade 70—79 and to 32.6% in the decade 80 and more);

— The prevalence of cerebral arteriosclerosis within overall cardiovascular diseases decreased in men from 10.1% in the decade 60—69 and 10.9% in the decade 70—79 to 6.7% in the decade 80 and more, whereas in women it increased from 8.5% in the decade 60—69 to 11.4% and 12.9% in the next 2 decades.

— In the case of heart failure the age-induced changes were not significant in men, whereas in women its prevalence within the cardiovascular pattern increased from 5.5% and 5.9% in the first 2 age-decades to 8.2% in the last decade.

— The prevalence of peripheral arteriosclerosis within the cardiovascular pattern was 5.1% in the decade 60—69 and increased to 9.8 and 9.3% in the next 2 decades in men; in women the age-induced changes were not significant.

THE STRUCTURE BY SEX AND AGE OF PATIENTS WITH ARTERIAL HYPERTENSION HOSPITALIZED IN THE NIGG IN 1979, ACCORDING TO ITS CLINICAL FORMS (Fig. 6)

Of the total number of patients hospitalized for AHT (516), 31.4% (162) were men and 68.6% (354) were women.

The distribution by age-decade was the following: 25.2% in the decade 60—69, 58.3% in the decade 70—79, and 16.5% in the decade 80 and more. The prevalence of AHT was 29.0%, 57.4% and 13.6%, respectively, in men and 23.4%, 58.8% and 17.8% in women.

The highest percentage occurred in patients hospitalized for essential AHT (70.4% in men and 57.6% in women), followed by the patients hospitalized for systolic AHT (22.2% in men; and 26.5% in women); the patients hospitalized for secondary AHT were on the third place (7.4% in men and 15.9% in women).

The analysis of the structure by age-decade according to the 3 clinical forms of AHT, pointed out the following facts:

— 91.5% of men aged 60—69 had essential AHT; the proportion decreased to 65.6% in the decade 70—79 and to 45.5% in the decade 80 and more. In the last decade the highest proportion (54.5%) was found in the patients with systolic AHT.

— In women, the highest prevalence of essential AHT (65.4%) was noticed in the decade 70—79, followed by the first (49.4%) and third (42.9%) decades. In the decade 80 and more, the patients hospitalized for systolic AHT prevailed (44.4%).

The increase with age in the proportion of patients with systolic AHT was statistically significant. Thus, while 6.4% of men and 20.5% of women aged 60—69 had systolic AHT, in the decade 70—79 the proportion increased to 22.6% and 23.6%, respectively, to reach 34.5% in men and 44.4% in women aged 80 and more; the prevalence increased more quickly in men than in women.

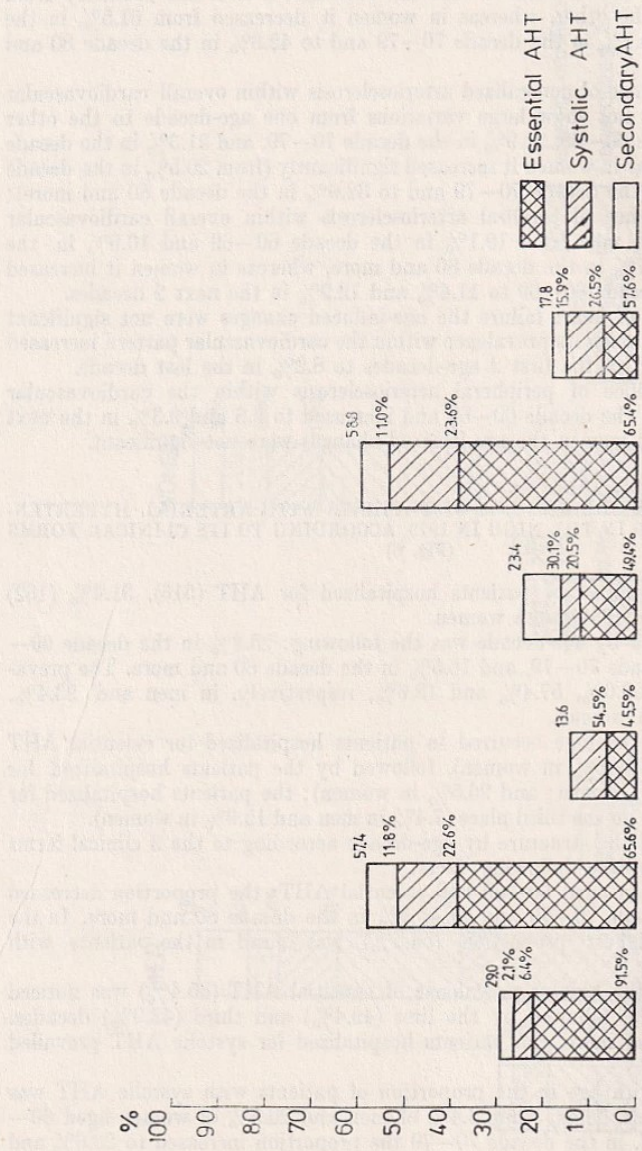


Fig. 6. — Structure by sex and age of the patients with AHT hospitalized in the NIGG in 1979, according to the clinical forms of AHT.

CONCLUSIONS

1. Cardiovascular and osteoarticular diseases had the highest prevalence among the causes of hospitalization. The average figure for cardiovascular diseases per one hospitalized aged patient was 1.5; 69.3% of the patients had osteoarticular diseases.

2. The analysis of prevalence by disease, sex and age-decade pointed out the structure and tendency of the cardiovascular clinical entities which had been the reasons for hospitalization.

3. The age-decade 70—79 had the heaviest pathological loading: 130.0 cardiovascular diseases per 100 patients: ischemic cardiopathy, cerebral arteriosclerosis, peripheral ischemia.

4. The prevalence of cardiovascular diseases within the general pattern of diseases increased with age from 37.5% in the decade 60—69 to 45.7% in the decade 80 and more.

5. AHT was the main clinical form in the hospitalized aged patients; with advancing age, systolic AHT became the dominant nosological background.

Résumé. Ce travail présente les données statistiques et épidémiologiques d'une recherche sur la structure de la morbidité due à la pathologie générale et surtout aux maladies cardio-vasculaires des personnes âgées et vieilles hospitalisées dans l'Institut national de gérontologie et gériatrie.

On a utilisé les méthodes statistiques.

Les causes principales de l'hospitalisation des personnes âgées sont tout d'abord les maladies de l'appareil circulatoire (42,0%) et puis les maladies du système ostéo-articulaire (19,7%).

L'analyse de la charge pathologique par rapport au nombre total de maladies chez les personnes de 60 ans et plus a révélé 351,7 maladies pour 100 personnes hospitalisées. Le groupe avec la charge pathologique la plus importante est celui des personnes de 80 ans et plus. Les maladies de l'appareil cardio-vasculaire sont les plus fréquentes, les valeurs les plus élevées étant constatées dans les groupes de 70—79 ans et de 80 ans et plus.

L'analyse de la charge pathologique cardio-vasculaire chez les patients âgés hospitalisés pour hypertension artérielle (HTA) a révélé la plus grande fréquence dans le groupe de 70—79 ans: 176,2 maladies cardio-vasculaires pour 100 malades à HTA.

Chez les femmes à HTA, la charge pathologique a été moins importante: 117,2 maladies cardio-vasculaires pour 100 patients hospitalisés par rapport à 149,0 chez les hommes.

Parmi les formes cliniques d'HTA, l'hypertension essentielle est la plus fréquente, priorité due aux deux premiers groupes d'âge (60—69 ans et 70—79 ans). A 80 ans et plus, l'HTA systolique se situe au premier plan.

REFERENCES

1. M. DUMITRU, *Bazele gerontocardiologiei*. Ed. medicală, Bucharest, 1979.
2. * * * *Etudes épidémiologiques des cardiopathies ischémiques*. Rapport d'un groupe de travail. Londres, 9—11 décembre 1968. Bureau régional de l'Europe, O.M.S., Copenhague.

ROMANIAN J. GERONT. GERIATRICS, 1981, 2, 1, p. 49–58

PHONOCARDIODYNAMIC STUDY IN THE AGED

LIDIA HARTIA, N. R. ZAMFIRESCU, AL. VRĂBIESCU

The National Institute of Gerontology and Geriatrics, Bucharest, Romania

Summary. The phonocardiogram, electrocardiogram and carotid sphygmogram were simultaneously recorded with a 6 NEK4 equipment in 55 aged subjects, 24 men (mean age 86.9 years) and 31 women (mean age 87.1 years). The clinical examination excluded the history of valvular diseases, either rheumatic or of other nature. Auscultation pointed out overt systolic murmurs in 8 men and 13 women.

In men, the phonocardiogram revealed 9 protosystolic and 4 holosystolic murmurs in the aortic area and 4 protosystolic and 6 holosystolic murmurs in the mitral area.

In women there were 14 aortic protosystolic, 6 aortic protomesosystolic and 4 aortic holosystolic murmurs. In the mitral area there were 13 protosystolic, 7 protomesosystolic and 2 holosystolic murmurs. The incidence of systolic murmurs was lower in the pulmonary artery area.

One of the problems raised by the impact of age on the heart is the presence of cardiac murmurs and their significance in the aged.

Usually, the subject's previous history does not include rheumatism (rheumatic carditis) or valvulopathy; if the murmur is best heard in the aortic area, it is frequently assigned to either calcified aortic stenosis or atherosclerosis, whereas if it is best heard in the apex area, it is assigned to mitral insufficiency.

Most of the data in literature on heart auscultation are connected to its application in congenital diseases and valvulopathies acquired early in life. Because of the increase in the aged population, heart auscultation has become ever more important [1]. Mention should be made that a series of signs are not equally important in the aged and young subjects [2, 3]. In 1976, Perez and Luisada [3] pointed out that, despite the relatively frequent cardiac murmurs after 60 years of age, the statistical studies on this problem are scarce. We found few such studies, too [1–7].

MATERIAL AND METHOD

The investigations were conducted on 55 subjects (24 men and 31 women) over 81 (average age: 86.9 with men — 81–94 years, and 87.1 with women — 81–100 years). Among them, only 9 men and 11 women were between 81 and 84. 30 subjects were longevous (85–100 years), 3 of the 24 men did not present major cardiac diseases; the rest suffered from ischemic cardiopathy, either painful or not, with ischemic electrocardiographic impairments, arterial hypertension with left ventricle hypertrophy electrocardiographically or radiologically evidenced.

In the group of women, only 3 patients did not present major heart diseases; the rest suffered from ischemic cardiopathy, either painful or not, with ischemic impairments, arterial hypertension and left ventricle hypertrophy.

The microphone for the phonocardiogram was placed on the most important auscultation areas: aortic and pulmonary areas and apex; the phonocardiogram was simultaneously recorded in 3 frequencies: 35, 70 and 140 Hz, with a 6-channel equipment (6 NEK4) with direct recording on paper. The electrocardiogram and carotid sphygmogram were simultaneously recorded with a piezoelectric transducer, taking into consideration the form (the anacrotic incisura for a possible aortic stenosis) and the ejection time of the left ventricle.

RESULTS

In the group of men, protosystolic murmurs were recorded in the aortic area of 9 patients and holosystolic murmurs in 4 patients; in the mitral area, protosystolic murmurs were pointed out in 4 patients and holosystolic murmurs in 6 patients. The incidence of systolic murmurs recorded in the pulmonary artery was lower (2 patients with holosystolic murmurs and one with telesystolic murmur). Ectatic ascending aortas were radiologically pointed out in 13 of the 24 patients. Presystolic gallop was discovered in 3 subjects. Overall incidence of murmurs in men was 59.4%.

In the group of women, the distribution of murmurs was the following:

In the aortic area, protosystolic murmurs were recorded in 14 patients, protomesosystolic murmurs in 6 patients and holosystolic murmurs in 4 patients.

In the mitral area, protosystolic murmurs were recorded in 13 patients, protomesosystolic murmurs in 7 patients and holosystolic murmurs in 2 patients.

In the pulmonary aortic area, protosystolic murmurs were recorded in 8 patients, mesosystolic in 2 patients and holosystolic in 4 patients. Presystolic gallop was present in 8 patients.

In the group of women the incidence of murmurs was 85.8%. Ectatic ascending aortas were present in 24 patients (67%).

9 subjects did not display systolic murmurs; 5 of these subjects were orthogerous (2 men and 3 women); only one of them presented a protosystolic murmur in the aortic and pulmonary artery area.

Ischemic cardiopathy either painful or not was prevalent in the cardiovascular pathology with cardiac involvement in non-orthogerous subjects, underlined, in some cases, by heart failure and arterial hypertension either with or without left ventricle hypertrophy and left ventricle loading.

The high incidence of ischemic and/or hypertensive cardiopathy in the patients under study may have contributed to the relatively increased percentage of systolic murmurs, particularly those in the mitral area which may be related to the papillary muscle dysfunction and heart failure.

Carotid sphygmogram did not point out any deviation in the anacrotic incisura indicating organic aortic stenosis; the ejection time of the left ventricle ranged within normal limits.

COMMENT

In young subjects with cardiac valvulopathy, the apical systolic murmur usually points to mitral insufficiency either anatomical or functional. The systolic aortic murmur indicates, in general, aortic stenosis, whereas the diastolic aortic murmur,

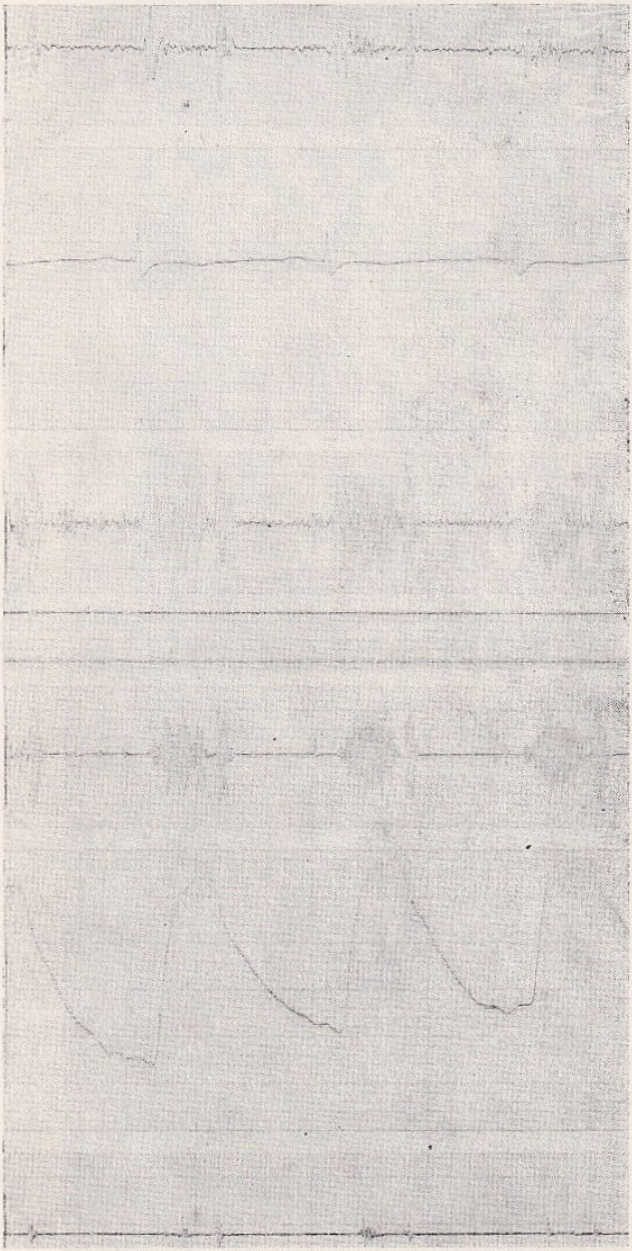


Fig. 1.—B.E., aged 100 (w.). Ischemic cardiopathy. 11.11.1979. Aortic holosystolic murmur.

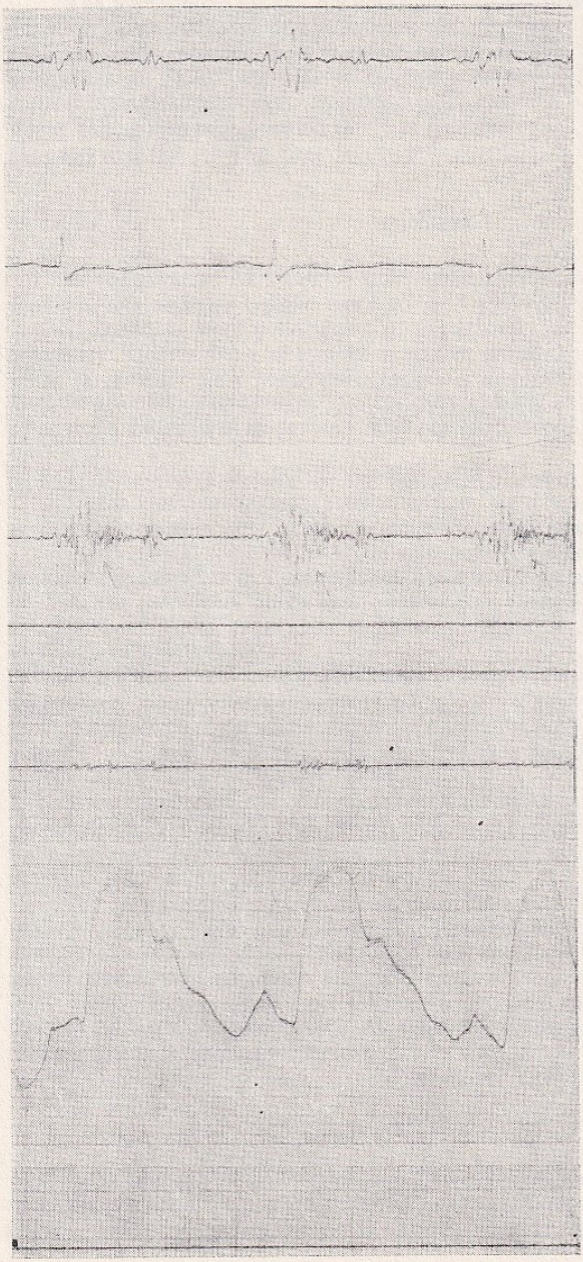


Fig. 2. — B.E., aged 100 (w.). Ischemic cardiopathy. 11.11.1979. Protosystolic murmur in the apex area.

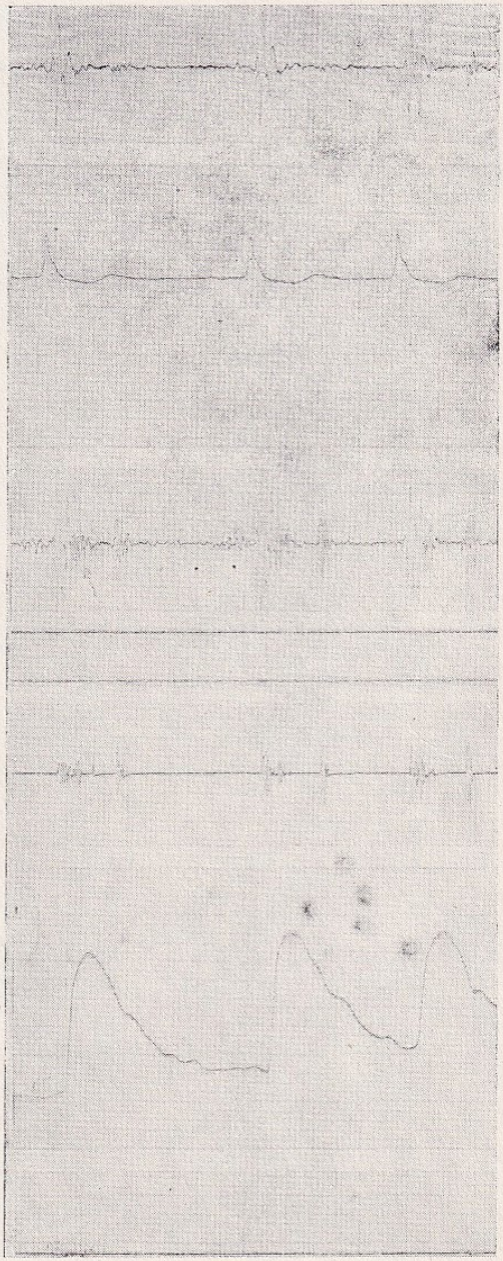


Fig. 3. — H.V., aged 94 (m.). Ischemic cardiopathy. 15.11.1979. Aortic proto-systolic murmur.

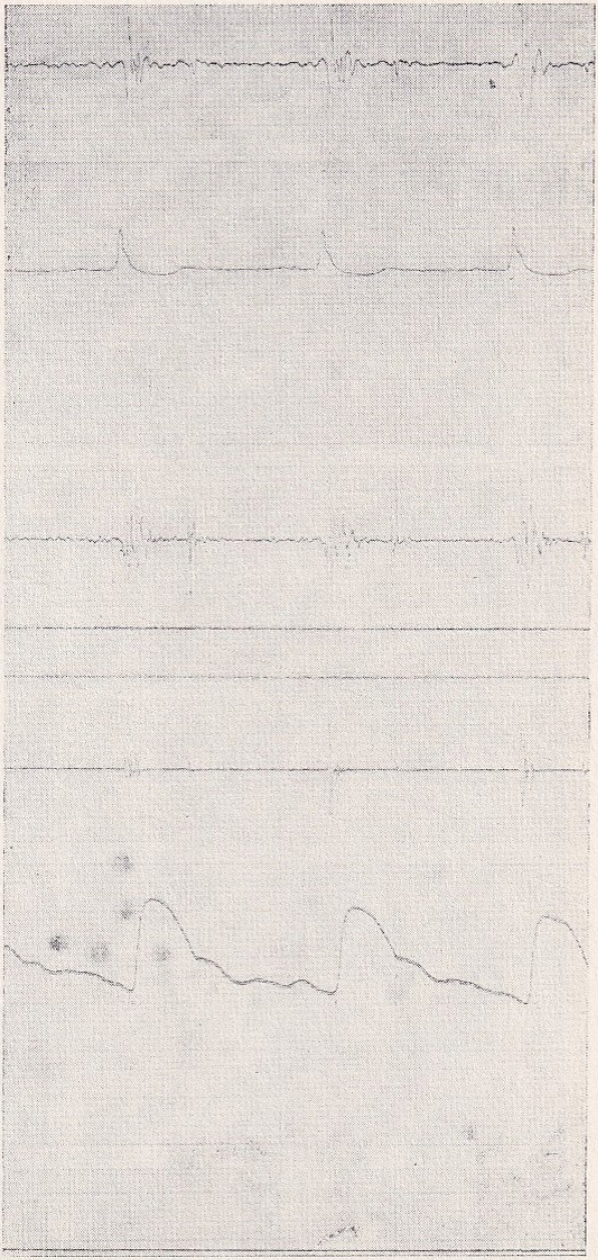


Fig. 4.—H.V., aged 94 (m.) Ischemic cardiopathy. 15.11.1979. Brief protosystolic murmur in the apex area.

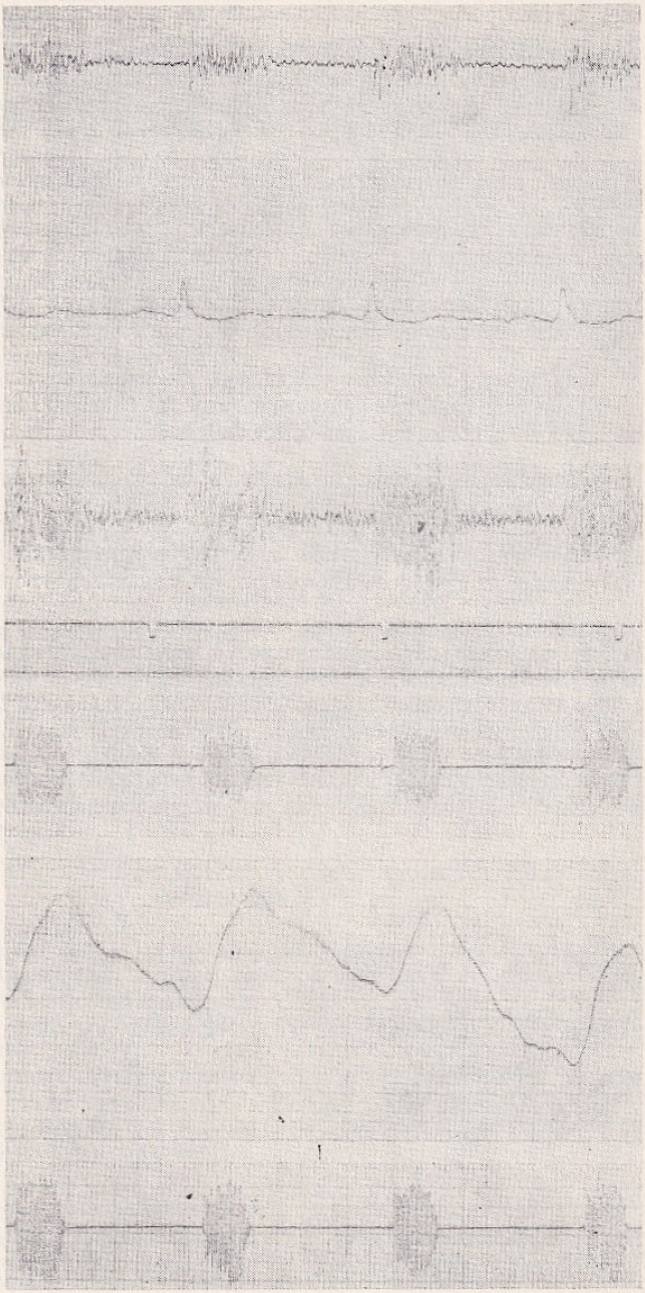


Fig. 5.—C.T., aged 89 (m.). Ischemic cardiopathy. 5.9.1980. Aortic holosystolic murmur.

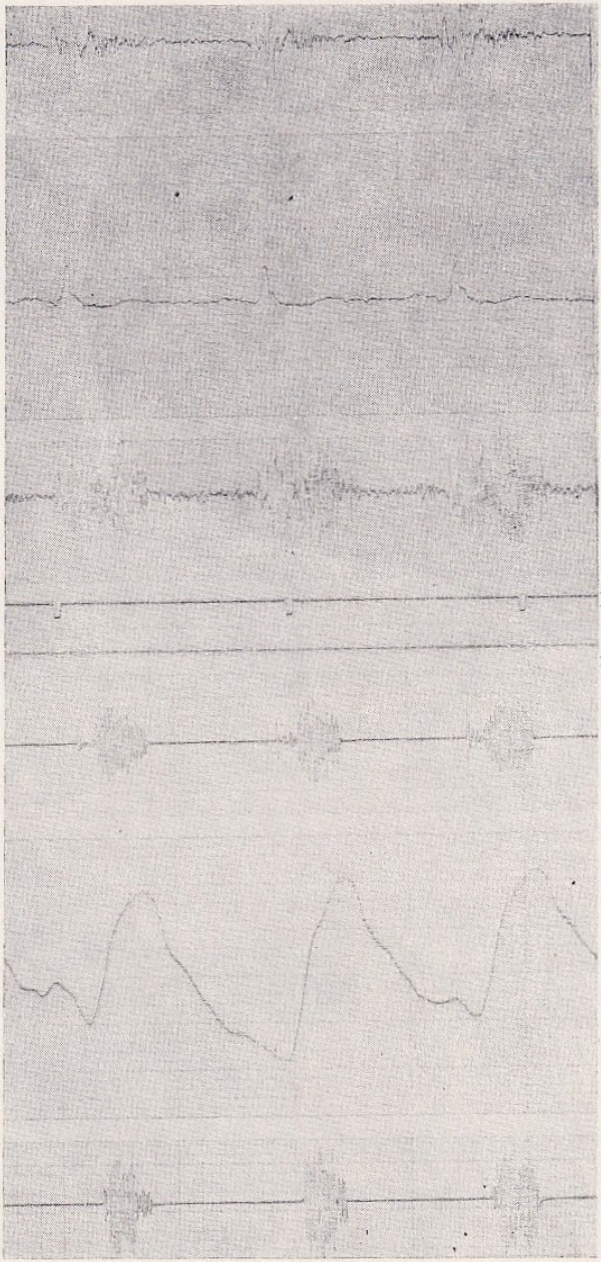


Fig. 6.—C.T., aged 89 (m.). Ischemic cardiopathy. 5.9.1980. Holosystolic murmur in the apex area.

aortic insufficiency. The apical diastolic murmur usually occurs in patients with mitral stenosis. In the aged, the origin of murmurs seems more complex.

An innocent systolic murmur (usually basal) may be induced by one of the following mechanisms:

— aortic enlargement;

— minimal fibrotic fusion of one or more commissures of the aortic valve without a significant reduction in the aortic surface;

— thickening and calcification of the sygmoid aortic valves, without important hemodynamic changes [1, 8, 9].

On auscultation, the murmur occurs in early or midsystole with an early peak, in contrast to the late peaking in organic stenosis. The carotid pulse tracing is normal in contour and duration and lacks the deep anacrotic notch and the slower rise typical of aortic stenosis [4].

Such cases did not display overt signs of left ventricle hypertrophy on the electrocardiogram and the size of the heart was normal under X-ray examination. These subjects did not present signs and symptoms specific to hemodynamic obstruction.

The generally accepted theory on the age-induced changes in the aortic valve advocates for their being the direct effect of increased hydrostatic pressure and turbulence [1, 9, 10].

The possible dilation of the ascending aorta caused by atherosclerosis should be taken into consideration since it induces the turbulence of the aortic blood flow, the so-called "relative aortic stenosis" [4].

Mention should be made that Perez and Luisada's [3] subjects did not display systolic murmurs of mitral insufficiency despite the changed heart rate or rhythm.

The fact supports the viewpoint according to which most of the mitral systolic murmurs are related to the dysfunction of the papillary muscle or to heart failure. In relation to this, Neurath [11] pointed out that the auscultatory phenomena leading frequently to the false diagnosis of mitral insufficiency in the aged are the result of either the dysfunction of the papillary muscle or mitral valve prolapse; an important part in making this diagnosis is played by the modern noninvasive techniques such as echocardiography.

CONCLUSIONS

The studies carried out so far have frequently pointed out systolic murmurs in aged women and men; their incidence increases with the most advanced ages, predominantly in the aortic and mitral areas.

The murmurs were particularly prevalent in the subjects suffering from ischemic cardiopathy.

The aortic murmurs can be generated by the ectasy of the aorta, whereas the apical murmurs can be caused by the dysfunction of the papillary muscle or by heart failure; they may be functional as in heart failure or/and organic as in the case of papillary muscle dysfunction.

Résumé. Chez 55 sujets âgés, 24 hommes (âge moyen 86,9 ans) et 31 femmes (âge moyen 87,1 ans), on a simultanément enregistré le phonocardiogramme, l'électrocardiogramme et le sphygmogramme, avec un appareil 6 NEK4. L'examen clinique a exclu des antécédents les affections

valvulaires rhumatiques ou d'autre nature. À la suite de l'examen on a constaté un souffle systolique non manifeste chez 8 hommes et 13 femmes.

Le phonocardiogramme a révélé chez les hommes, dans le foyer aortique, la présence d'un souffle protosystolique chez 9 cas et d'un souffle holosystolique chez 4 cas, mais dans le foyer de la mitrale on a constaté 4 cas à souffle protosystolique et 6 cas à souffle holosystolique.

Chez les femmes on a constaté dans l'aorte un souffle protosystolique chez 14 cas, un souffle protomésosystolique chez 6 cas et un souffle holosystolique chez 4 cas. Dans le foyer de la mitrale on a constaté un souffle protosystolique chez 13 cas, un souffle protomésosystolique chez 7 cas et un souffle holosystolique chez 2 cas. Dans la zone de l'aorte pulmonaire on a constaté une incidence plus réduite des souffles systoliques.

REFERENCES

1. B. L. SEGAL, W. LIKOFF, *Heart sounds and murmurs in the aged.* Geriatrics, **22,** *3*, 1967, 149.
2. T. H. HOWELL, *Cardiac murmurs in old age: a clinico-pathological study.* J. Amer. Geriat. Soc., **15,** *6*, 1967, 509.
3. G. L. PEREZ, A. A. LUISADA, *Incidence of murmurs in the aged heart.* J. Amer. Geriat. Soc., **24,** *1*, 1976, 29.
4. C. ARAVANIS, A. A. LUISADA, *Obstructive and relative aortic stenosis. Differential diagnosis by phonocardiography.* Amer. Heart J., **54,** *1*, 1957, 32.
5. C. S. BETHEL, E. W. CROW, *Heart sounds in the aged.* Amer. J. Cardiol., **37,** *4*, 1963, 763.
6. E. T. DAVISON, S. A. FRIEDMAN, *Significance of systolic murmurs in the aged.* New Engl. J. Med., **279,** *5*, 1968, 225.
7. D. H. SPODICK, V. M. OUARRY PIGOT, *Fourth heart sound as a normal finding in older persons.* New Engl. J. Med., **288,** *3*, 1973, 140.
8. D. L. BRUNS, L. G. VAN DER HAUWERT, *The aortic systolic murmur developing with increasing age.* Brit. Heart J., **20,** *3*, 1968, 370.
9. A. POMERANCE, *Aged changes in human heart valves.* Brit. Heart J., **29,** *2*, 1967, 222.
10. J. B. McMILLAN, M. LEV, *The aging heart. II. The valves.* J. Geront., **19,** *1*, 1964, 1.
11. O. NEURATH, *Cardiovascular changes in/of old age.* J. Amer. Geriat. Soc., **26,** *6*, 1978, 286.

ROMANIAN J. GERONT. GERIATRICS, 1981, 2, 1, p. 59–66

PECULIARITIES OF ATRIAL ARRHYTHMIAS IN THE AGED

S. COTOI

The Institute of Medicine, First Medical Clinic, Tîrgu Mureş, Romania

Summary. The study was conducted on 46 patients aged 60—82 presenting various atrial arrhythmias: 18 cases of atrial fibrillation, 6 cases of atrial flutter, 4 cases of atrial tachycardia with block, 10 cases of chaotic atrial arrhythmia, and 8 cases of intra-atrial conduction disturbances. Particular aspects of atrial arrhythmias occur in terms of both evolution and response to treatment, as a result of the decrease in the active myocardial mass and electrophysiological disturbances underlying the aging process. The above mentioned peculiarities are discussed and exemplified in the present paper.

The aged persons suffering from chronic cardiovascular and pulmonary diseases often display complex atrial arrhythmias with particular aspects in point of manifestation and response to treatment [1, 2, 3, 4].

The diseases of the sinus node and atrioventricular conduction system are considered among the capital factors in the pathogenesis of atrial arrhythmias, such as myocardial ischemia, diffuse or focal fibrosis, and myocardial distension [5, 6, 7].

In the course of the last 5 years, 46 patients over 60 with arrhythmias were followed up at the coronary care unit of the medical clinic 1 in Tîrgu Mureş. The object of the present paper was the study of the peculiar aspects in these arrhythmias.

MATERIAL AND METHOD

Of the material available at the clinic, 46 atrial arrhythmias were selected, which occurred in patients aged 60—82. In the group under study the women (25 patients) were not significantly prevalent.

The following methods were used to study the arrhythmias: electrocardiographic monitoring over variable periods of time, recording of atrial intracavitary electrogram, His's potential, atrial monophasic action potential, atrial electrostimulation and transesophageal electrogram.

The authors investigated and followed up 18 patients with atrial fibrillation, 6 patients with atrial flutter, 4 patients with atrial tachycardia with block, 10 patients with chaotic atrial arrhythmia, and 8 patients with intra-atrial conduction defects.

RESULTS

Of the 18 patients with atrial fibrillation, self-limitation of fibrillation was noticed in 6 patients, with the spontaneous transition to sinus rhythm in 2 cases, chaotic atrial arrhythmia in 3 cases and atrial paralysis with junctional rhythm in one case. In all the cases mentioned above the hemodynamic aspect did not

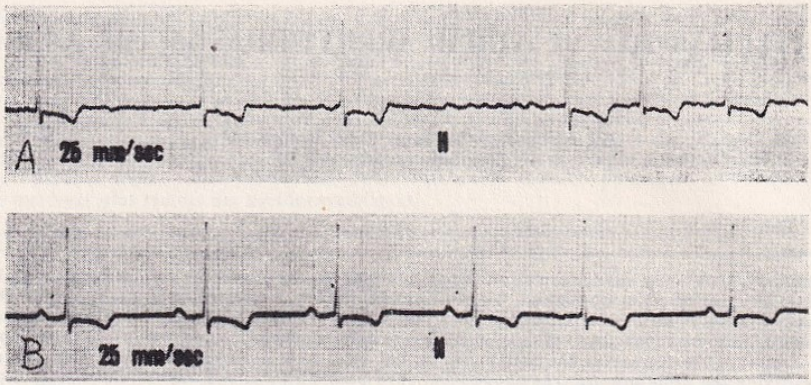


Fig. 1. — Standard ECG lead II, in panel A during atrial fibrillation, in panel B (in sinus rhythm) after spontaneous cessation of arrhythmia.

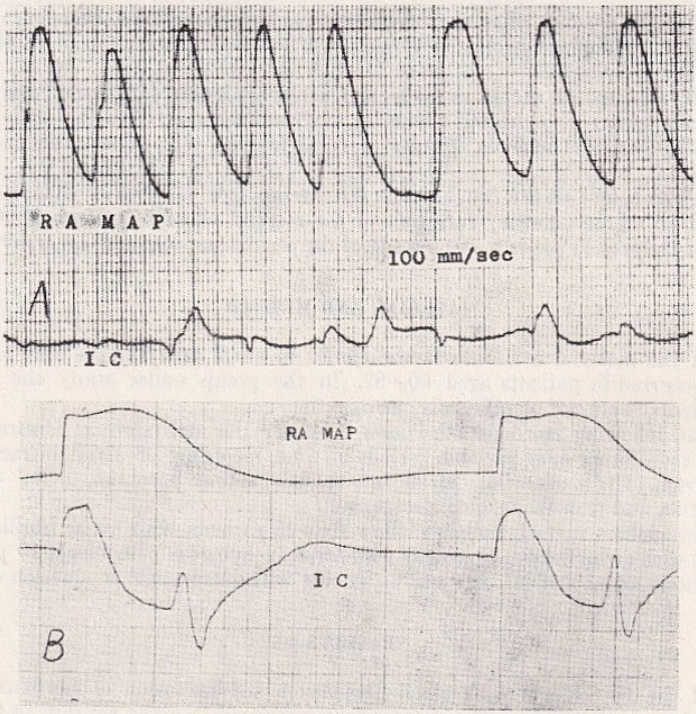


Fig. 2. — Simultaneous recording of monophasic action potential (RAMAP) and intracavitary (IC) atrial recording: *A*, during atrial fibrillation; *B*, in sinus rhythm. Same patient as in figure 1.

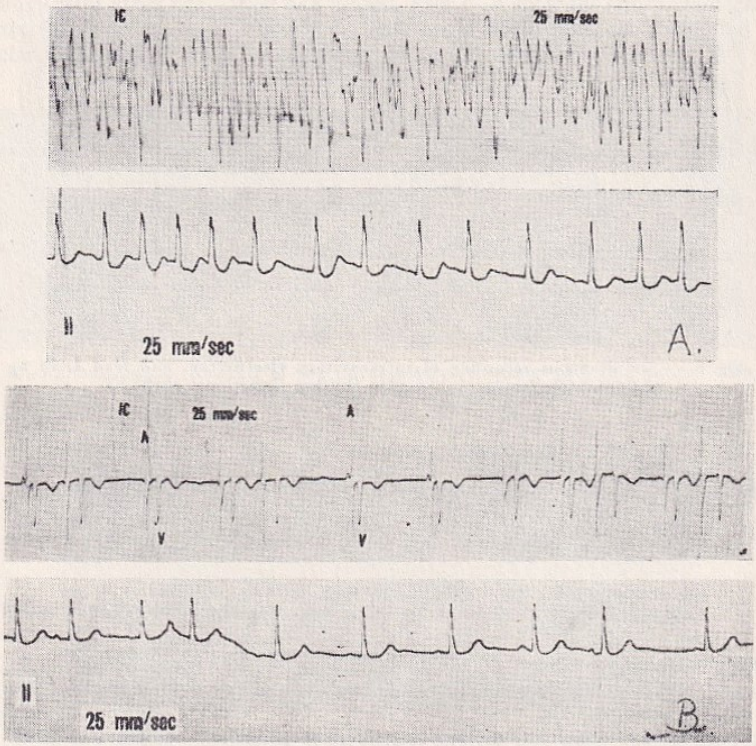


Fig. 3. — *A*, The upper strip is the intracavitary recording, the lower strip the ECG lead II, during atrial fibrillation; *B*, the same recordings after spontaneous transition of atrial fibrillation to chaotic atrial arrhythmia.

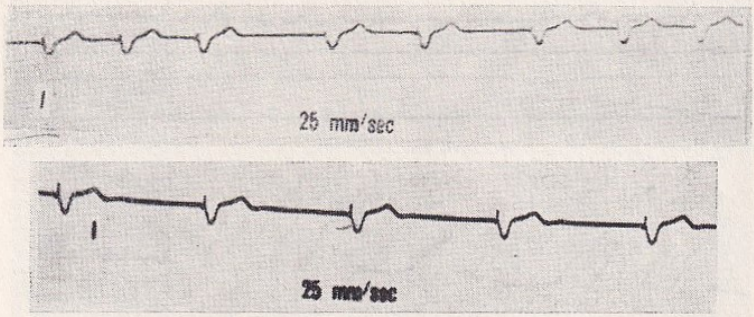


Fig. 4. — In the upper panel atrial fibrillation, and in the lower one junctional rhythm with atrial standstill after spontaneous cessation of atrial fibrillation.

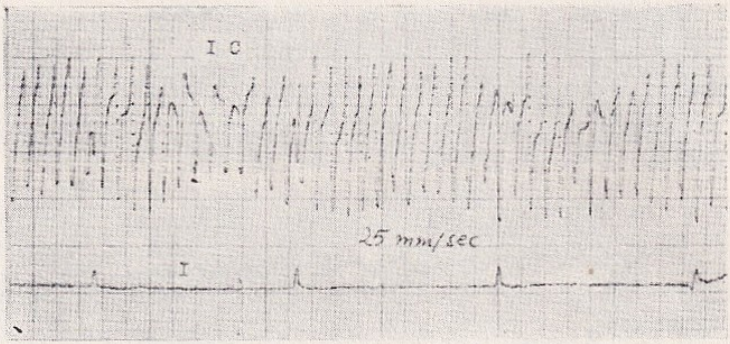


Fig. 5. — Simultaneous recording of intracavitary electrogram and lead I, in a patient with regular ventricular rhythm (junctional rhythm).

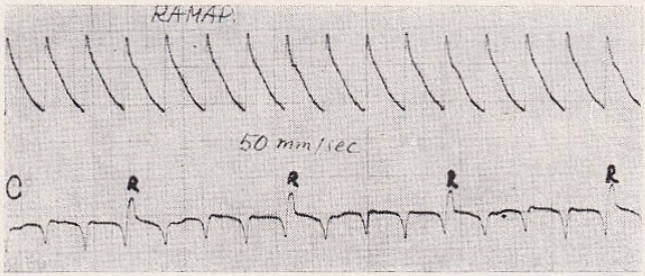


Fig. 6. — Simultaneous recording of monophasic action potential (RAMAP) and intracavitary lead in a patient with atrial flutter and regular ventricular rhythm (R).

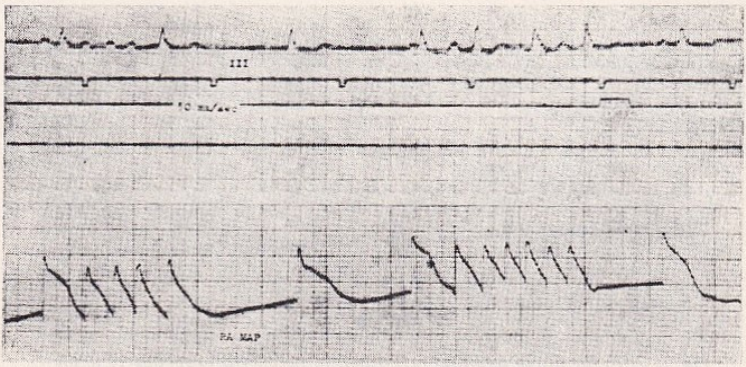


Fig. 7. — Simultaneous recording of lead III and monophasic action potential (RAMAP) in a patient with self-limitation of atrial flutter.

improve after atrial fibrillation had ceased. Figs 1—4 show the electrocardiographic aspects of these cases. In other 4 patients atrial fibrillation was associated with regular junctional rhythm without signs of digital overdosing (Fig. 5).

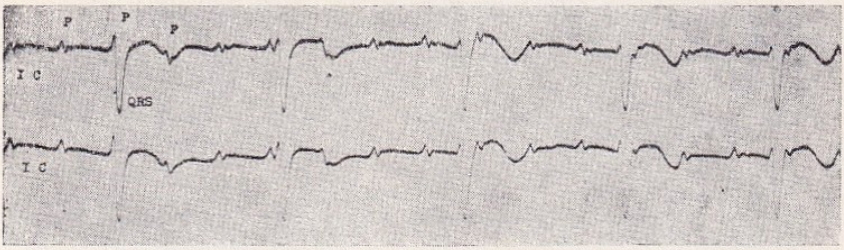


Fig. 8. — Simultaneous recording of two intracavitary recordings (IC) in a patient with atrial tachycardia with block and regular ventricular rhythm.

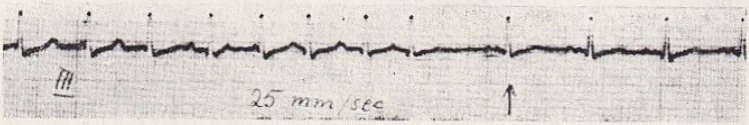


Fig. 9. — Cessation of atrial tachycardia with block during intravenous of administration Aslavital. The arrow points to the first sinusal complex.

4 of the patients with atrial flutter displayed regular ventricular rhythms (Fig. 6); in 2 patients, arrhythmias, although easily triggered, ceased spontaneously (Fig. 7).

2 of the patients suffering from atrial tachycardia with block had regular ventricular rhythm (Fig. 8). 4 patients were treated with Aslavital administered intravenously. The arrhythmia ceased during the administration of the drug; this effect was maintained using one Aslavital vial i.m. daily. Fig. 9 shows the cessation of atrial tachycardia with block.

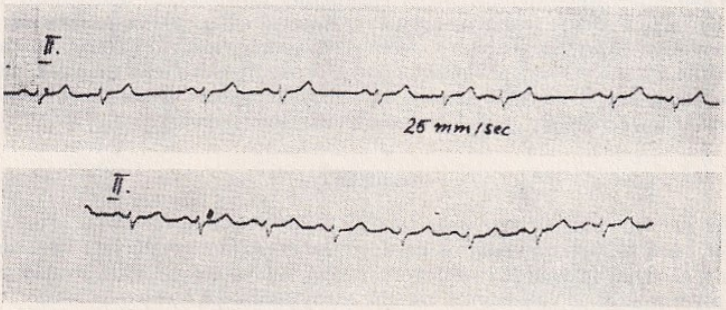


Fig. 10. — Transition of a chaotic atrial arrhythmia (upper panel) to normal sinus rhythm (lower panel) after Aslavital given intravenously.

In 8 of 10 patients with chaotic atrial arrhythmia the conversion to sinus rhythm occurred as a result of intravenous, then intramuscular xyline injections. Recently we used Aslavital at first intravenously, then one i.m. vial daily as maintenance therapy. Fig. 10 shows the effect of Aslavital.

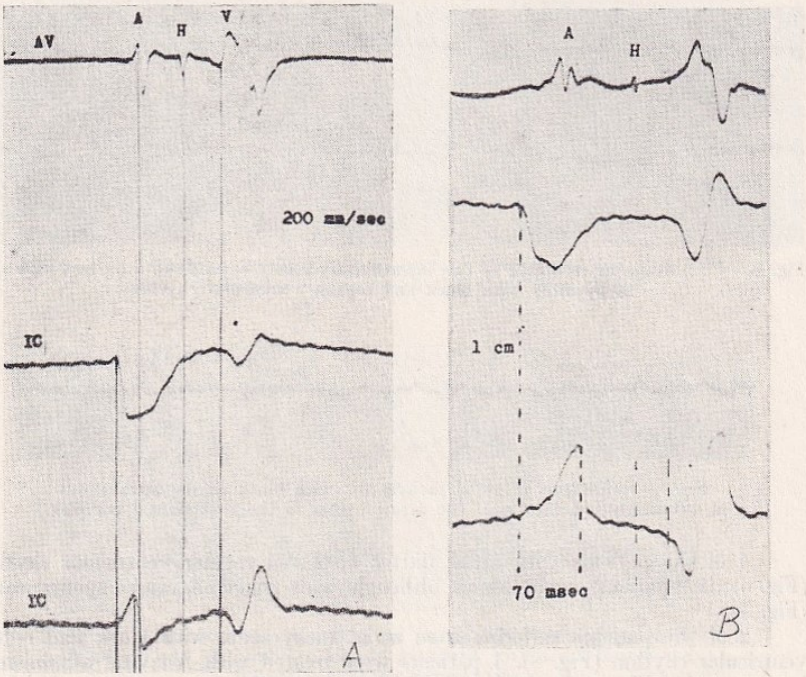


Fig. 11. — Intra-atrial conduction disturbance demonstrated by an intracavitary technique: *A*, normal value; *B* lengthening of intra-atrial conduction. H = His's bundle potential.

8 patients displayed intra-atrial conduction disturbances manifesting themselves by large P waves and prolonged P-Q intervals. Fig. 11 shows one of these cases investigated by intracavitary electrocardiography using 3 electrode catheters.

Although the diseases of the sinus and atrioventricular nodes were not included in this study, fig. 12 shows 3 electrocardiographic aspects of the interrelationship between atrial arrhythmias and the above mentioned nodes.

COMMENT

As known, some predisposing conditions are required for atrial arrhythmias to occur, such as a certain relation between the excitation conduction time and the duration of atrial myocardial refractory period, and a certain critical mass of the atrial myocardium as substratum for the arrhythmias [2, 8, 9].

The self-limitation of old fibrillation, the occurrence of chaotic atrial arrhythmias of tachycardias with block, and the self-limitation of atrial flutter are partly

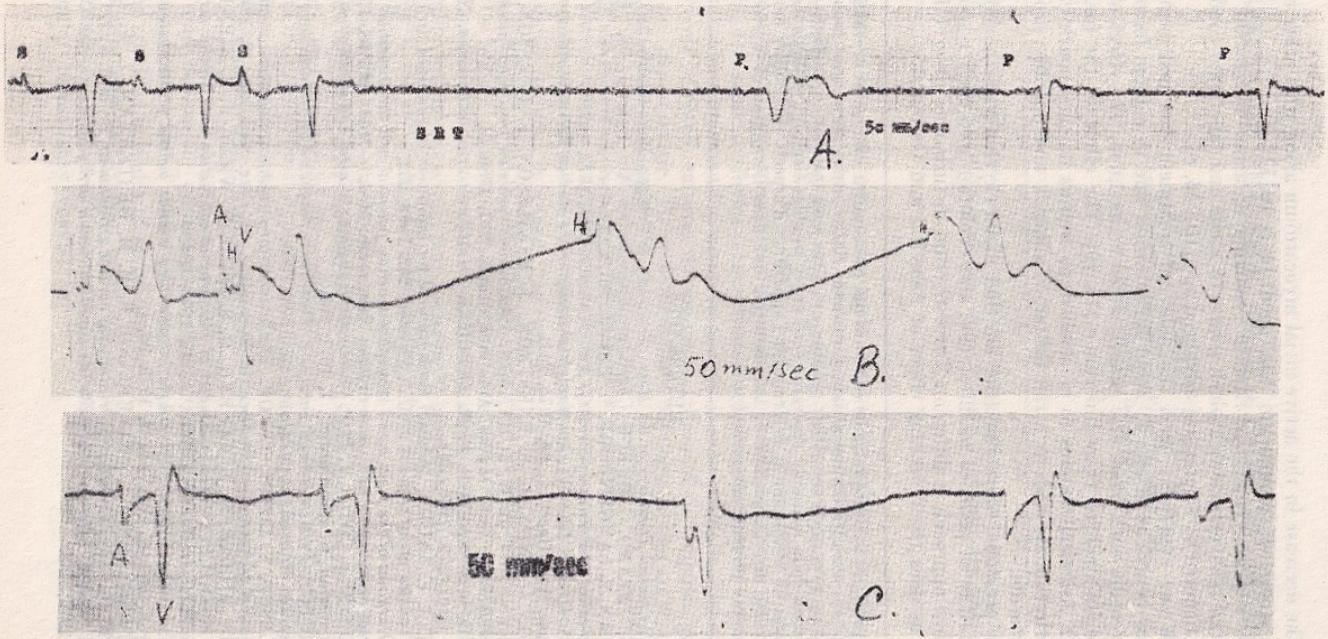


Fig. 12 — Atrial arrhythmias secondary to sinus node and atrioventricular node disturbances: *A*, long sinus node recovery time after rapid atrial pacing (S = stimulus); *B*, spontaneous junctional rhythm shown by His's bundle electrogram recording; *C*, atrioventricular dissociation shown on transesophageal electrocardiogram.

the result of the decrease in the active atrial myocardium along with other electrophysiological processes common in the aged [4, 5, 10, 11].

The slow regular ventricular rhythm occurring in atrial fibrillation, atrial flutter and atrial tachycardia with block points to atrial and junctional conduction disturbances triggered by sclerosis in advanced age [10—13, 8].

Although our experience with the Aslavital treatment has just begun, we maintain it has beneficial effects in atrial arrhythmias due to ectopic focus, such as atrial tachycardia with block and chaotic atrial arrhythmia. The effect of Aslavital seems to be stronger than Lidocain's [14, 15]. The effect of the long-term treatment with Aslavital remains to be studied, as well as its therapeutic efficacy in re-entry arrhythmias, such as atrial flutter, fibrillation and possibly supraventricular tachycardia.

The data presented allow the assertion that atrial rhythm disturbances have several peculiarities in point of manifestation and evolution and their response to the therapeutical approach is different. These rhythm disturbances deserve further investigation, as does the promising effect of Aslavital and Gerovital.

Résumé. On a étudié 46 patients entre 60 et 82 ans qui présentaient différentes arythmies atriales, à savoir: 18 cas avec fibrillation atriale, 6 cas avec flutter atrial, 4 cas avec tachycardie atriale à bloc, 10 cas avec arythmie atriale chaotique et 8 cas avec troubles de conduction intra-atriale. La réduction de la masse du myocarde actif et les troubles électrophysiologiques secondaires au processus de vieillissement déterminent l'apparition d'aspects particuliers des arythmies atriales, autant dans la manière de manifestation que dans l'évolution et la réponse au traitement. Ce travail présente ces aspects particuliers.

REFERENCES

1. S. BELLET, *Clinical Disorders of the Heart Beat.* Lea & Febiger, Philadelphia, 1971.
2. I. PHILIPS, I. SPANO, G. BURCH, *Chaotic atrial mechanism.* Am. Heart J., **78,** 1969, 171.
3. B. M. KAPLAN, R. LANGENDORF, M. LEV, A. PICK, *Tachycardia-bradycardia syndrome (so-called sick sinus syndrome).* Am. J. Cardiol., **31,** 1973, 497.
4. S. COTOI, S. DRĂGULESCU, *Complex atrial arrhythmias studied by suction electrode technique.* Am. Heart J., **90,** 1975, 241.
5. G. B. OLSSON, G. ONDAHL, S. ENESTROM, J. ESKILSSON, S. PERSSON, M. L. GRENNERT, B. W. JOHANSON, *Spontaneous reversion from long lasting atrial fibrillation to sinus rhythm.* Acta med. scand., **207,** 1980, 5.
6. K. I. SHINE, I. A. KASTOR, P. M. JURCHAK, *Multifocal atrial tachycardia.* N. Engl. J. Med., **279,** 1968, 344.
7. T. C. WEST, J. F. LAUDA, *Minimal mass required for indication of sustained arrhythmias in isolated atrial segment.* Am. J. Physiol., **202,** 1962, 232.
8. S. COTOI, *Duration of the right atrial monophasic action potential and the transition between atrial arrhythmias and sinus rhythm.* Rev. roum. Méd. — Méd. int., **18,** 1980, 83.
9. S. GAVRILESCU, S. COTOI, T. POP, *Chaotic atrial rhythm. Clinical and electrophysiological observation.* G. ital. Cardiol., **1,** 1971, 388.
10. S. COTOI, T. POP, *Persistent atrial paralysis. Three cases diagnosed by intracavitary electrogram* (in Romanian). Med. int., **25,** 1973, 1005.
11. S. GAVRILESCU, S. COTOI, T. POP, *The endocavitary electrocardiographic exploration in atrial tachycardia with block* (in Romanian). St. Cerc. Med. int., **13,** 1972, 395.
12. R. N. SCOTT MILLAR, B. J. MAURER, D. S. REID, R. WRAY, J. S. BIRKHEAD, J. P. SHILLINGFORD, *Studies of intraarterial conduction with bipolar atrial and His electrograms.* Brit. Heart J., **35,** 1973, 604.
13. S. COTOI, S. DRĂGULESCU, *A simple intracavitary bedside method for estimation of the P—R interval.* Cor Vasa, **2,** 1975, 96.
14. F. H. N. SPRACKLEN, J. J. KIMERLING, E. M. M. BESTERMAN, J. W. LICHTFIELD, *Use of Lidocaine in treatment of cardiac arrhythmias.* Br. med. J., **1,** 1968,89.
15. S. COTOI, C. LUCA, *Effects of Lidocaine on supraventricular arrhythmias.* G. ital. Cardiol., **6,** 1976, 433.

ROMANIAN J. GERONT. GERIATRICS, 1981, 2, 1, p. 67–72

ASPECTS OF THE SICK SINUS SYNDROME IN THE AGED

MARIA REPOLSKI, S. COTOI

The Institute of Medicine, First Medical Clinic, Tîrgu Mureş, Romania

Summary. 22 patients aged over 60 with sick sinus syndrome are presented and discussed in the light of the data existing in the specialty literature. Diagnostic and treatment peculiarities in the aged are emphasized.

During the last years, sinus node dysfunction gained recognition as the cause of various myocardial rhythm disturbances, raising difficult problems of diagnosis and treatment. Its first description, due to Lown (1967), involved electrically defibrillated patients. The diagnostic criteria were established by Ferrer [1, 2] and comprise a large spectrum of clinical manifestations due to sinus node dysfunction [3, 4]. Sinus dysfunction may be of minor importance, expressed only by moderate sinus bradycardia, when the patient is asymptomatic. The sinus node may be severely affected, causing the complete failure of the impulse generator; such cases are symptomatic. The varied symptomatology is due to secondary cardiac and cerebral dysfunctions, a defective perfusion being their triggering factor. The syncope is the severest form of the sick sinus syndrome.

The sick sinus syndrome is relatively frequent in medical practice. It prevails in the pathology of the aged, with the highest incidence in the seventh decade [4] and is more frequent in women. Its various symptoms often raise problems of differential diagnosis. Most of the signs are the result of a decreased perfusion through the vital organs, triggered by the low ventricular frequency or tachyarrhythmias [3]. The cerebral symptoms (dizziness, intermittent memory disturbances, insomnia, irritability, paresis, syncope) may be wrongly interpreted. Myocardial manifestations may either be absent or appear as palpitations, signs of heart failure and angina pectoris.

Ischemic heart disease has been reported as the most frequent cause of the disease (50%) [3], sclerotic-degenerative processes are present in 30–35% of the patients, and myocardial rheumatic diseases, cardiomyopathy, congenital diseases, surgical traumas, arterial hypertension, pericarditis, myocarditis, malignant processes have been mentioned among other causes.

Various rhythm disturbances occur depending on the severity of the sick sinus syndrome. In 75–80% of the patients the clinical picture is dominated by sinus bradycardia, the earliest form of the disease, followed by sinus stop, sinoatrial block, long atrial pause following atrial extrasystoles, chronic atrial fibrillation, or repeated episodes of atrial fibrillation with slow ventricular frequency, etc. The bradycardia-tachycardia syndrome occurs in advanced sick sinus syndrome. Beside supraventricular disturbances, atrioventricular conduction defects and intraventricular blocks may coexist [5].

If sick sinus syndrome is suspected because of clinical and electrocardiographic signs, the following additional investigations are required to make a definite diagnosis: 24-hr monitoring, revealing data on bradycardia (mostly during the night) and tachycardia episodes. The sinus stop exceeding 3 seconds following the compression of the carotid sinus is suggestive of sick sinus syndrome. In patients with this syndrome the heart rate remains below 90 beats/min after the Valsalva test or dosed muscular exercise.

Whereas the response of sinus bradycardia to atropine is tachycardia, in the patients with sick sinus syndrome, after 0.5—1 mg atropine i.v., the heart rate remains below 90 beats/min.

The electrophysiological studies aimed at determining sinus node recovery time, respectively sino-atrial conduction time by rapid atrial pacing [6, 7, 8] are quite important for an accurate diagnosis. The absence of the sinus rhythm after the conversion of atrial fibrillation has a diagnostic value.

MATERIAL AND METHOD

Of 56 patients with sick sinus syndrome, diagnosed according to the above-mentioned criteria, 22 patients (12 men and 12 women) were selected, aged 60—81.

The investigations were conducted at the laboratory of the First Medical Clinic of Tîrgu Mureş [9, 10]. Ischemic cardiopathy was the underlying disease in 21 patients; one patient suffered from mitro-aortic disease of rheumatismal etiology. The Adams-Stokes syndrome was present in 7 patients, angina pectoris in 15, heart failure in 12, chronic or paroxysmal atrial fibrillation in 14 patients. Carotid sinus compression was often a characteristic of the disease. Atropine, belladonna preparations (Foladon), beta-stimulating agents (Astmopent, Alupent) were administered and their effect monitored. Intracavitary investigations were carried out in 10 patients, the sinus node recovery time being prolonged (1,230—2,600 m/sec). Defibrillation was applied unsuccessfully in 8 patients.

RESULTS AND COMMENT

Here are some representative cases studied by the authors.

Case 1. — T.M., aged 60, woman, diagnosis: mitro-aortic disease of rheumatismal etiology.

The patient presents supraventricular tachycardia with block, atrial flutter with variable block and rapid conduction episodes having untoward hemodynamic consequences because of which electric defibrillation was decided. Complex rhythm and conduction disturbances followed after 200 w/sec: bradycardic sinus rhythm, tachycardia, atrioventricular dissociation, coronary sinus rhythm, junctional rhythm, Wenckebach sino-atrial block, explained in the context of the sick sinus syndrome. The association of the antiarrhythmic therapy resulted in the stabilization of the bradycardic sinus rhythms with junctional lapses (Figs 1, 2).

Case 2. — Sz.M., aged 74, woman, diagnosis: ischemic cardiopathy, sick sinus syndrome.

The patient presents heartbeat disorders, dyspnoea under exertion, loss of consciousness.

The basic rhythm is sinus bradycardia with stops, tachycardic flaps, probably reentrant tachycardia. The prolonged sinus recovery time confirmed the diagnosis (Figs 3, 4).

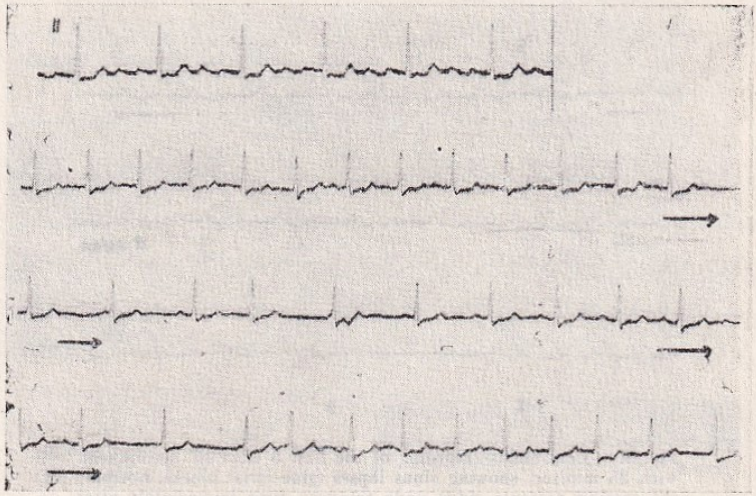


Fig. 1. — Recording in continuous tracing of the second lead, with 25 mm/sec. Passage from atrial flutter with regular ventricular response (upper tracing) to junctional tachycardia, atrioventricular dissociation and junctional tachycardia (the other 3 tracings).

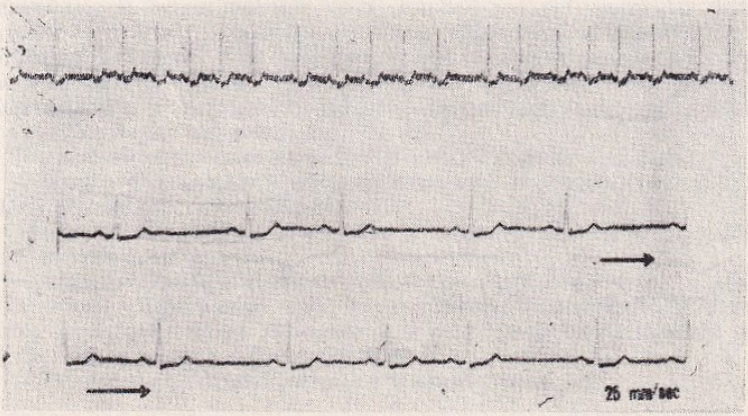


Fig. 2. — Continuation of the recording in fig. 1. Tachycardia with block (first tracing) which passes into sinus rhythm with sino-atrial block (next tracings).

Case 3. — G.A., aged 65, man, diagnosis: ischemic cardiopathy, chronic atrial fibrillation with slow rhythm, heart failure.

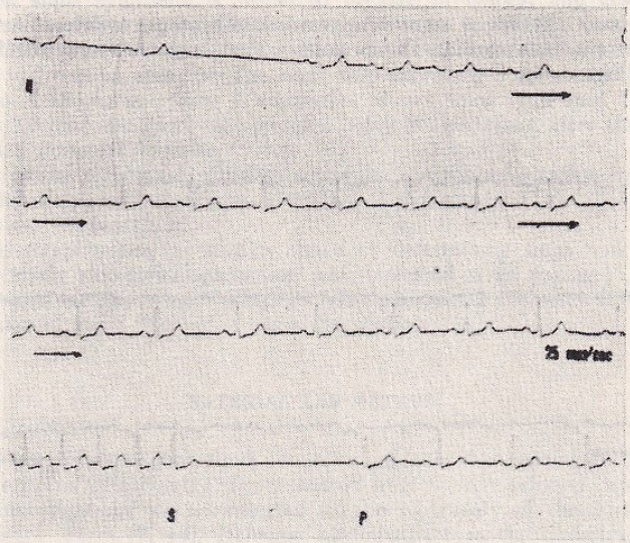


Fig. 3. — Continuous recording of the first 3 tracings, second lead with 25 mm/sec, showing sinus lapses (sino-atrial block). Bottom: the tracing presents sinus node recovery time immediately after pacing (S = stimulus).

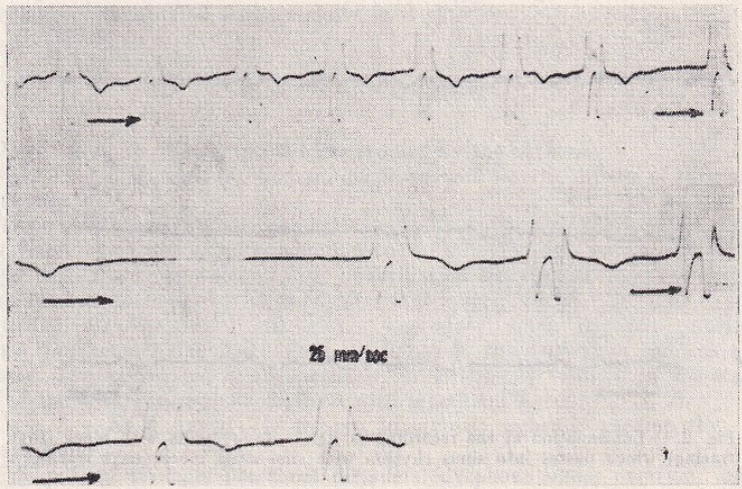


Fig. 4. — Continuous right atrial intracavitary recording, showing sinus lapses.

Chemical defibrillation with quinidine was tried because of the impaired hemodynamic condition. Cardiac arrest subsequent to quinidine ingestion, which responded to external cardiac massage. Cardiac performance reinitiated, sinus bradycardia occurred (20—40 beats/min), with repeated Adams-Stokes attacks.

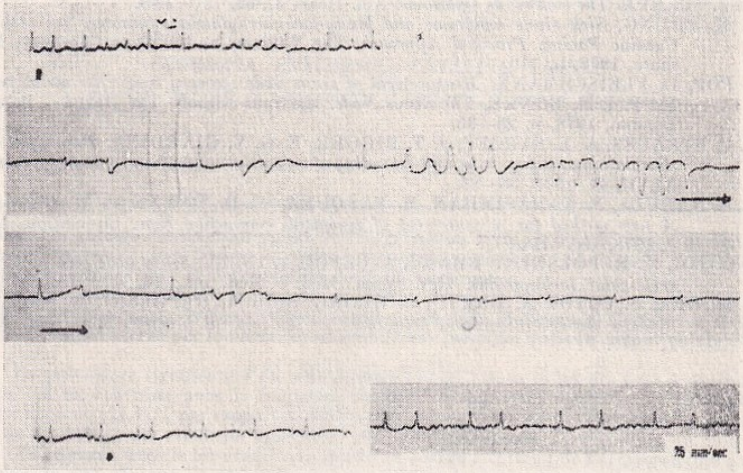


Fig. 5. — Upper tracing shows atrial fibrillation. The next tracings show sinus bradycardia, junctional beats, ventricular tachycardias (peak-moulding). Bottom: the left tracing shows right atrial stimulation: the right tracing shows the reappearance of atrial fibrillation.

Administration of beta-stimulating agents resulted in rapid ventricular rhythms, ventricular tachycardia, ventricular fibrillation which required repeated electrical defibrillation. Temporary right atrial pacing with a catheter and an external pacemaker was required to maintain efficient cardiac performance. The patient had cardiogenic shock. During pacing, the patient's condition improved, and 24 hrs later atrial fibrillation was reinitiated (Fig. 5).

The analysis of the cases investigated revealed the following aspects:

— Sinus node pathology is relatively frequent in the aged and raises difficult problems of diagnosis and treatment.

— Rhythm disorders are more difficult to bear in the aged, Adams-Stokes attacks occur frequently.

— Atrial fibrillation is relatively frequent as a late manifestation of the sick sinus syndrome; defibrillation may result in severe postconversional disorders requiring immediate technical assistance; it is a risk factor higher than the steady atrial fibrillation, prior to defibrillation.

— The use of an artificial pacemaker is usually successful.

Résumé. On présente et l'on analyse 22 patients au-dessus de 60 ans, qui s'intègrent dans les critères de la maladie du noyau sinusal, conformément aux données fournies par la littérature. On souligne les particularités de diagnostic et de traitement de ce groupe d'âge.

REFERENCES

1. M. I. FERRER, *The sick sinus syndrome in atrial disease.* J.A.M.A., **206,** 1968, 645.
2. M. I. FERRER, *The sick sinus syndrome.* Circulation, **XLVII,** *47*, 1973, 635—641.
3. A. J. MOSS, R. J. DAVIS, *Brady-tachy syndrome.* Progr. cardiovasc. Dis., **16,** 1974, 439.
4. W. J. SCARPA, *The sick sinus syndrome.* Am. Heart J., **92,** 1976, 648.
5. E. K. CHUNG, *Sick sinus syndrome and brady-tachyarrhythmia syndrome.* In: *Artificial Cardiac Pacing. Practical Approach.* The Williams and Wilkins Company, Baltimore, 1978, p. 119.
6. T. POP, D. FLEISCHMANN, *Measurement of sinus node recovery time after atrial pacing.* In: F. I. M. BONKE, *The Sinus Node.* Martinus Nijhoff, The Hague — Boston — London, 1978, p. 23—35.
7. H. C. STRAUSS, A. L. SAROFF, J. T. BIGGER, E. G. V. GIARDINA, *Premature atrial stimulation as a key to the understanding of sinoatrial conduction in man.* Circulation, **XLVII,** *47*, 1973, 86—93.
8. O. S. NARULA, S. NARASIMHAN, M. VASQUEZ, W. D. TOWNE, J. W. LINHART, *A new method for measurement of sinoatrial conduction time.* Circulation, **LVIII,** *4*, 1978, 706—714.
9. S. COTOI, M. REPOLSKI, A. BRATU, A. CEPOI, A. INCZE, *Sinus node reentrant supraventricular tachycardias.* Rev. roum. Méd. — Méd. int., **16,** *3*, 1978, 251—253.
10. C. DUDEA, S. COTOI, A. BRATU, C. GEORGESCU, M. REPOLSKI, E. CARASCA, *Modern electrocardiographic techniques in the medical practice.* Med. Rev., **XXIV,** *1*, 1978.

ROMANIAN J. GERONT. GERIATRICS, 1981, 2, 1, p. 73–83

CORRÉLATIONS CLINIQUES ET BIOLOGIQUES CONCERNANT LES HYPERLIPOPROTÉINÉMIES, LA THROMBOPHILIE ET L'ATHÉROSCLÉROSE CHEZ LES PERSONNES ÂGÉES

GEORGETA ENĂCHESCU, CĂTĂLINA LÖSNER

Institut National de Gérontologie et Gériatrie, Bucarest, Roumanie

Résumé. Les auteurs étudient sur un lot de 185 personnes âgées de 60 à 88 ans, à dyslipidémie, les aspects corrélatifs concernant les types d'hyperlipoprotéinémie (HLP) et la thrombophilie, par rapport à l'incidence et à l'évolution de l'athérosclérose.

On a relevé l'incidence augmentée (57,90%) des cas à thrombophilie, parmi les sujets âgés à HLP (phénomènes évidents surtout chez les âgés de la 7e décennie) ainsi que la fréquence significativement accrue des facteurs thrombophiliques parmi les patients à HLP mixte du type IIb.

La prévalence significative du sexe féminin (77,9%) dans le lot des âgés à dyslipidémie étudiés est en contraste avec la fréquence significativement plus élevée de la thrombophilie chez les hommes (71,47% par rapport à 53,80% chez les femmes). Le fait correspond à l'accroissement de l'incidence des accidents vasculaires chez les hommes âgés.

En relevant dans le lot étudié une incidence accrue (75,10%) de l'athérosclérose avancée du point de vue clinique, la recherche n'a pas mis en évidence des corrélations significatives entre le type d'HLP, d'un côté, et l'incidence et la localisation clinique prédominante de la maladie, de l'autre côté.

La recherche porte sur l'HLP et la thrombophilie, comme facteurs de risque importants dans l'évolution et les complications des lésions athérosclérotiques, jusqu'aux âges avancés.

Sans diminuer la grande importance du diagnostic précoce et surtout de la prévention primaire des lésions athérosclérotiques chez les jeunes et les adultes on impose le concept, mentionné souvent dans la littérature de spécialité et soutenu par les progrès scientifiques dans le domaine des affections dégénératives cardio-vasculaires, selon lequel le problème de la thérapie de l'athérosclérose et surtout la prévention de ses complications thrombotiques porte notamment sur le 3e âge [1].

Les conceptions classiques concernant les lésions athérosclérotiques définitives après un certain âge et donc l'inutilité de l'approche thérapeutique antiathéro-sclérotique chez les âgés, doivent être remaniées, si on prend en considération la multitude des faits expérimentaux et anatomo-cliniques présentés à l'appui d'une éventuelle réversibilité et surtout de la progression des lésions athérosclérotiques, jusqu'aux âges très avancés [2], [3], [4], [5], [6], [7]. La diminution du calibre des petites artères et des artérioles se développant avec l'âge, d'une manière plus régulière que les lésions d'athérosclérose, empire sensiblement sur les conséquences de ces dernières.

Les arguments qui démontrent que les multiples facteurs athérogènes, thrombogènes et générateurs d'ischémie continuent à exercer leur action sur la paroi vasculaire (en dépit des mécanismes compensatoires, compatibles à une évolution fonctionnelle favorable, dans les conditions de l'existence des lésions à l'âge d'environ 60 ans) étant responsables de multiples complications cliniques de l'athéro-

sclérose chez les âgés et justifiant l'intérêt tout spécial pour les différentes modalités thérapeutiques antiathérosclérotiques au 3e âge [8], [9].

Tenant compte de ce qu'on a présenté jusqu'ici, cette étude renferme la détermination des corrélations cliniques et biologiques concernant l'hyperlipoprotéinémie HLP et la thrombophilie, par rapport à l'incidence et à l'évolution de la maladie athéromateuse, chez les personnes âgées au-dessus de 60 ans.

MATÉRIEL ET MÉTHODES

On a investigué, par l'intermédiaire de l'examen clinique et des tests humoraux hématologiques et biochimiques, 185 patients âgés de 60 à 88 ans, dont 143 femmes et 42 hommes.

Le critère principal et obligatoire pour la sélection des patients a été la présence de l'hyperlipémie (HL): hypercholestérolémique, hypertriglycéridémique ou mixte.

1. Pour le diagnostic initial de triage de l'HL et pour le diagnostic biochimique ultérieur — selon la classification de l'OMS [10] — du type d'HLP, on a utilisé les suivants tests de laboratoire:

— La lipidémie totale (méthode gravimétrique).
Valeurs normales: 450—700 mg. % ml. ser.

— La cholestérolémie totale (méthode de Rappaport).
Valeurs normales: 190—260 mg. % ml. ser.

— La triglycéridémie (méthode de Tixier et Claude).
Valeurs normales: 100—150 mg. % ml. ser.

— Le rapport cholestérol/triglycérides.
Valeurs normales: 1,80—1,85.

— L'appréciation de l'aspect du sérum après la conservation pendant 24 heures à la température de +4°C.

— L'électrophorèse des lipoprotéines sériques (lipidogramme en agarose, à la séparation de 4 fractions de lipoprotéines et leur détermination en pourcents, selon la courbe d'intégration).
Valeurs normales: alphalipoprotéines: 26%±4;
prébêtalipoprotéines (VLDL) : 17%±4;
bêtalipoprotéines (LDL) : 57%±4;
chilomicrons : absents.

— Le calcul du taux de cholestérol, de LD et de VLDL, selon les formules usuelles.
Valeurs normales: Ch (LDL) = 135—170;
Ch (VLDL) = 24—27.

2. Afin de pouvoir apprécier le type de thrombophilie, on a appliqué les suivants tests hématologiques:

a) pour la thrombophilie plasmatique (par hypercoagulation):

— le thrombélastogramme (r + k).
Valeurs normales: 25—40 mm.

— l'indice de tolérance à l'héparine *in vitro*.
Valeurs normales: 0,8—1,2.

b) pour la thrombophilie par hyperfonctionnalité thrombocytaire.
(hypercoagulabilité du type structural).

— le thrombélastogramme (am).
Valeurs normales: 50—60 mm.
— L'activité thrombodynamique thrombocytaire.
(méthode thrombélastographique).
Valeurs normales: 20—30 mm.
— L'indice d'agglutinabilité thrombocytaire à l'ADP.
(méthode de Veiner, modifiée par De Nicola).
Valeurs normales: 5—7.

c) pour la thrombophilie par déficit d'anticoagulants physiologiques:
— L'héparinémie endogène (méthode de Pieptea).
Valeurs normales: 5—8 u/ml.

d) pour la thrombophilie plasmatique par hypofibrinolyse.
Le temps de la lyse du caillot (méthode thrombélastographique).
Valeurs normales: 60—100 minutes.

Les examens cliniques répétés et les explorations fonctionnelles effectuées à chaque patient ont établi le stade évolutif de l'athérosclérose et la localisation prédominante de la maladie du point de vue clinique.

RÉSULTATS

L'évaluation du point de vue statistique des données a relevé les résultats présentés schématiquement dans les tableaux et les graphiques ci-joints.

1) On distingue la prévalence significative des femmes, du point de vue statistique par rapport aux hommes, dans le lot des patients à dyslipidémie étudiés, ainsi que la prévalence significative de l'HL et de l'HLP parmi les patients âgés des deux sexes appartenant à la 7e décennie (fig. 1).

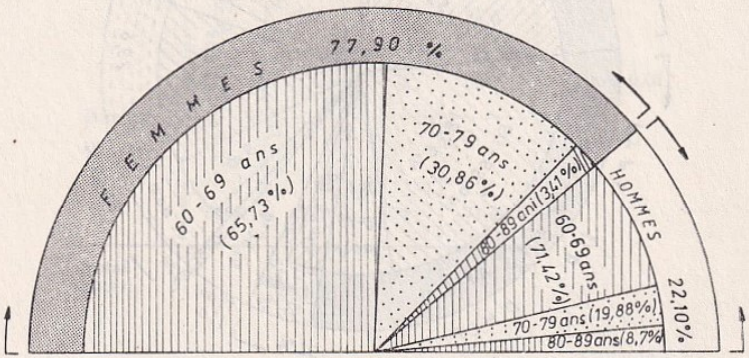


Fig. 1. — Le taux des sujets âgés à HLP par rapport au sexe et à la décennie d'âge.

2) Le diagnostic du type d'HLP a relevé la prévalence nette du type IV, pour le lot examiné suivi en ordre décroissant par le type IIb, l'apparition du type IIa et du type V d'HLP étant sporadique (tableau 1, fig. 2).

Tableau 1

La répartition des patients âgés investigués par rapport à l'âge, au sexe et au type d'HLP

Le type d'HLP	N° des cas	Femmes			Hommes		
		60—69 ans	70—79 ans	80—89 ans	60—69 ans	70—79 ans	80—89 ans
I	—	—	—	—	—	—	—
IIa	6	4	2	—	—	—	—
IIb	63	46	9	—	6	—	2
III	—	—	—	—	—	—	—
IV	115	43	32	6	24	8	2
V	1	1	—	—	—	—	—
Total	185	94	43	6	30	8	4

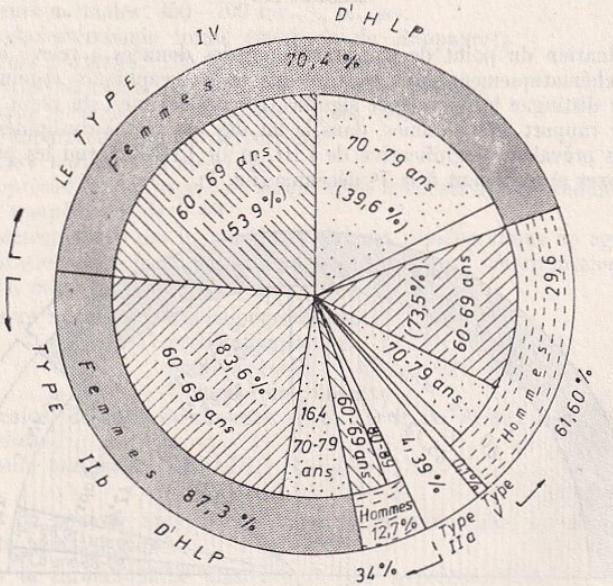


Fig. 2. — Le taux des sujets âgés investigués par rapport à l'âge, au sexe et au type d'HLP.

3) On remarque aussi, l'incidence élevée (57,9%) des cas à thrombophilie (plasmatique, thrombocytaire ou mixte) parmi les sujets âgés à HL et HLP étudiés (tableau 2), phénomène évident surtout dans la 7e décennie. En effet, 78% des patients âgés à HLP et thrombophilie simultanée appartiennent à la 7e décennie.

4) La prévalence significative des femmes en ce qui concerne l'incidence de l'HLP est en contraste, dans le lot étudié, avec la prévalence significative des hommes, en ce qui concerne l'incidence de la thrombophilie (tableau 2, fig. 3). Tandis que les femmes représentent 77,9% des patients à HLP étudiés, l'incidence de la thrombophilie est significativement accrue chez les hommes (71,42%), par rapport à celle des femmes (53,84%). L'incidence la plus élevée de la thrombophilie (90%) appartient aux hommes de la 7e décennie.

Tableau 2

L'incidence de la thrombophilie parmi les sujets âgés investigués, par rapport à l'âge et au sexe

Groupes de sujets à HLP	Âge	N° des cas	Cas à thrombophilie plasmatique thrombocytaire ou mixte		Signification statistique
			Valeur absolue	%	
Femmes	60 69	94	57	60,6	
	70 79	43	20	46,5	
	80 89	6	—	—	
	Total	143	77	53,84	←
Hommes	60 69	30	26	86,6	
	70 79	8	4	50	$p < 0,01$
	80 89	4	—	—	
	Total	42	30	71,42	←
Total général		185	107	57,9	

5) La thrombophilie est surtout réalisée par l'hyperfonctionnalité thrombocytaire, par déficit d'anticoagulants physiologiques et par l'hypofibrinolyse, moins fréquents étant les cas à thrombophilie par hypercoagulabilité plasmatique globale.

6) L'étude de la corrélation entre le type d'HLP et la thrombophilie démontre l'incidence significativement accrue de la thrombophilie (68,25%) pour le type IIb de l'HLP, par rapport au type IV d'HLP, où cette incidence est de 54,40%

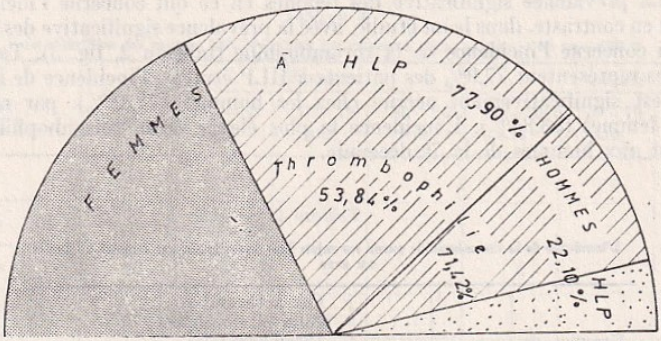


Fig. 3. — La corrélation HLP — thrombophilie — sexe, parmi les sujets âgés investigués.

Tableau 3

Corrélation entre le type d'HLP et la thrombophilie plasmatique thromboeytaire ou mixte dans le lot des sujets âgés investigués

Le type d'HLP	Nº des cas			Cas à thrombophilie plasmatique thromboeytaire ou mixte			Signification statistique
	Femmes	Hommes	Total	Femmes	Hommes	Total	
IV	81	34	115	36	23	59 (51,4%)	← $p < 0,01$
IIb	55	8	63	36	7	43 (68,2%)	←
IIa	6	—	6	4	—	4	
V	1	—	1	1	—	1	
Total	143	42	185	77	30	107	

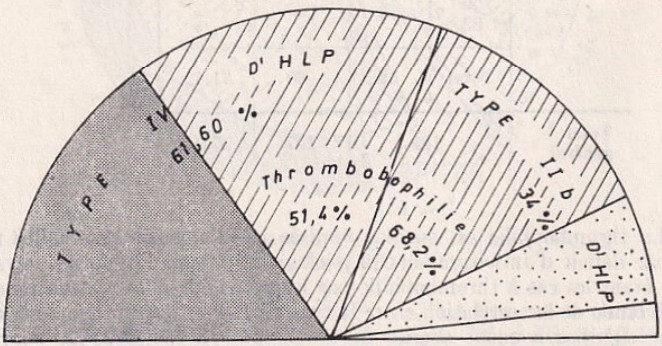


Fig. 4. — La corrélation type HLP — thrombophilie, aux principaux types d'HLP chez les sujets âgés investigués.

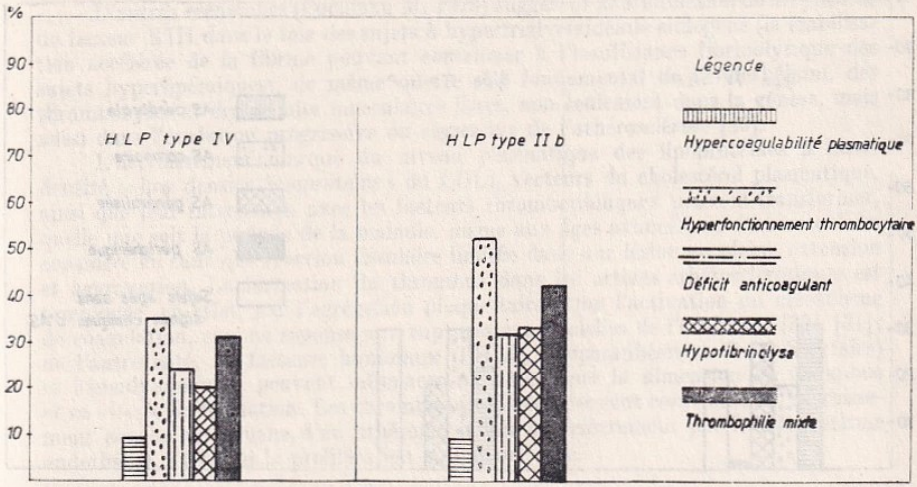


Fig. 5. — Le taux des valeurs pathologiques des indicateurs thrombophiliques, aux principaux types d'HLP chez les sujets âgés investigués.

(tableau 3, fig. 4). On a démontré aussi l'accroissement significatif du taux des valeurs pathologiques des indicateurs thrombophiliques, chez les personnes âgées à HLP de type IIb, par rapport aux patients du type IV d'HLP (fig. 5).

7) Les corrélations des données cliniques et humorales ont mis en évidence l'incidence élevée (75,1%) des cas avec athérosclérose avancée du point de vue clinique, chez les personnes âgées à HLP investiguées (tableau 4), la fréquence des séquelles des accidents vasculaires (cérébraux ou coronaires) étant de 5,2%. On n'a pas signalé de différences significatives entre les hommes et les femmes ou entre les principaux types d'HLP (IIb et IV), d'un côté, et l'incidence et la localisation

Tableau 4

La fréquence des cas d'athéroscléroze (AS) manifeste du point de vue clinique, chez les patients âgés à ALP

Le type d'HLP	Nº des cas	Nº des cas d'AS cliniquement manifeste		Signification statistique	Cas d'accidents vasculaires		Signification statistique
		Val. absolue	%		Val. absolue	%	
IV	115	90	78,3	← n.s.	8	6,9	← n.s.
IIb	63	44	70,0	←	4	6,3	←
IIa	6	5	83,0		—	—	
V	1	—	—		—	—	
Total	185	139	75,1		12	6,5	

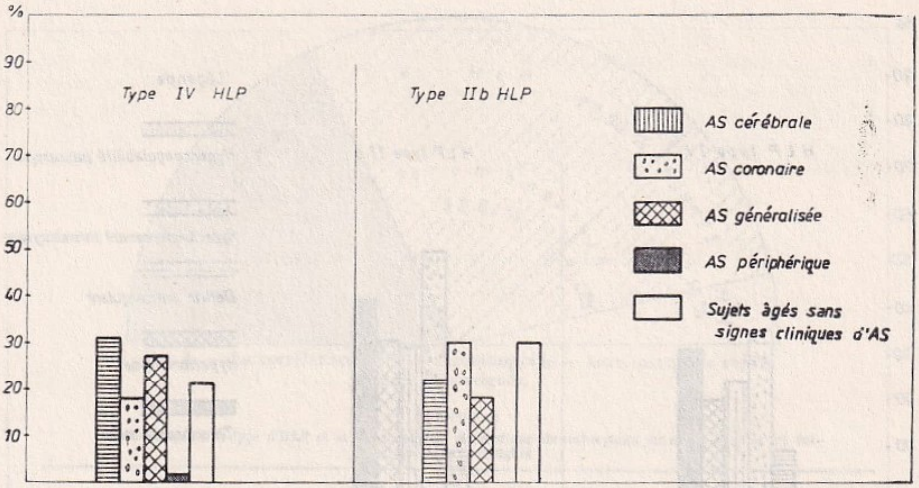


Fig. 6. — La fréquence des manifestations cliniques d'athérosclérose chez les patients à HLP des type IV et IIb.

prédominante de la maladie du point de vue clinique, de l'autre côté (tableau 4, fig. 6).

On relève que 80% des accidents vasculaires ont été signalés chez les patients hommes.

DISCUSSIONS

Si on prend en considération l'incidence élevée de la thrombophilie chez les sujets âgés à HLP investigués, de même que la fréquence relativement importante d'HL et d'HLP chez les âgés au-dessus de 60 ans, on peut apprécier que ces deux catégories de facteurs de risque vasculaire continuent à exercer leur action sur la paroi artérielle en favorisant l'extension et l'aggravation des lésions athéroscléro-tiques jusqu'aux âges avancés. Conformément à cette conception ainsi qu'à celle de la réversibilité des lésions athérosclérotiques (en conditions humorales favorables), [12], [13], [14], [15], les interrelations des facteurs de risque dislipidémiques et throm-bophiliques acquièrent la même importance tant pour l'évolution de l'athérosclérose du 3e âge, que pour les âges plus jeunes.

Une relation évidente entre l'incidence des thromboses et l'accroissement de l'agglutinabilité thrombocitaire a été mise en évidence dans la période consécutive aux interventions chirurgicales, ainsi que dans d'autres situations « thrombogènes », comme l'athérosclérose, le diabet sucré, les maladies vasculaires, oclusives, l'hémo-cistinurie, etc. [16], [17], [18], [19], [20], [21]. De nombreux auteurs ont constaté une concentration élevée des lipides plasmatiques chez les patients à thrombose [22], [23], [24], une action stimulatrice des sels sodiques des acides gras à longue chaîne [25], des phospholipides purifiées et des bêtalipoprotéines sur l'agrégation thrombocytaire à l'ADP et thrombine [26], ainsi que des corrélations étroites entre l'agrégation thrombocytaire et le processus de coagulation par l'intermédiaire du mécanisme de la libération du facteur 3 thrombocytaire [27], [28].

D'autres recherches (Cucuianu M. 1973) suggèrent la stimulation de la synthèse du facteur XIII dans le foie des sujets à hypertriglycéridémie endogène (la stabilisation accélérée de la fibrine pouvant contribuer à l'insuffisance fibrinolytique des sujets hyperlipémiques), de même que le rôle fondamental de l'endothélium, des thrombocytes et des cellules musculaires lisses, non seulement dans la génèse, mais aussi dans l'évolution progressive ou régressive de l'athérosclérose [29].

L'accroissement marqué du niveau plasmatique des lipoprotéines à basse densité (« low density lipoproteins » ou LDL), vecteurs du cholestérol plasmatique, ainsi que leur interaction avec les facteurs thrombophiliques peuvent transformer, quelle que soit la période de la maladie, même aux âges avancés, un état vasculaire considéré en tant que réaction tissulaire limitée dans une lésion en pleine extension et aggravation. La formation du thrombus dans les artères athérosclérotiques est provoquée, en effet, par l'agrégation plaquettaire et/ou l'activation du mécanisme de coagulation, comme réponse aux ruptures superficielles de l'athérome [30], [31]; de l'autre côté, les facteurs humoraux (l'HLP, l'hyperadhésivité thrombocytaire) et hémodynamiques peuvent influencer ou déterminer la dimension du thrombus et sa vitesse de formation. Les thromboses répétées peuvent contribuer à l'accroissement couche sur couche d'un athérome induit antérieurement par le traumatisme endothélial, l'HLP et la prolifération musculaire lisse.

CONCLUSIONS

1) L'association fréquente de principaux facteurs humoraux de risque dans l'apparition des complications vasculaires athérosclérotiques, chez les sujets au-dessus de 60 ans, constitue un argument à l'appui de la conception actuelle concernant les possibilités de l'évolution et de l'aggravation de ces lésions, jusqu'aux âges avancés.

2) Sous aspect clinique et humoral, on remarque trois phénomènes:

a) L'accroissement de la fréquence de l'HL et de l'HLP chez les femmes âgées, par rapport aux hommes de même âge.

b) L'accroissement significatif de la thrombophilie (plasmatique, thrombocytaire ou mixte) chez les hommes âgés à HLP, fait qui correspond à l'accroissement de l'incidence des accidents vasculaires chez ceux-ci, par rapport aux femmes de même âge.

c) L'incidence élevée des facteurs thrombophiliques pour les cas à HLP mixte (le type IIb).

3) L'interférence, le conditionnement réciproque et l'accumulation des effets vasculaires des facteurs dyslipidémiques, thrombophiliques plaquettaires et éventuellement hémodynamiques peuvent expliquer les phases évolutives, progressives ou régressives des lésions athérosclérotiques, chez les âgés.

4) L'établissement des facteurs humoraux de risque individuels s'impose, comme objectif pratique, afin de déterminer le pronostic et d'améliorer l'efficacité thérapeutique, dans l'athérosclérose des personnes âgées.

Summary. The authors investigated on a sample of 185 elderly, aged 60—88, with dyslipidemia, the correlative aspects concerning the types of hyperlipoproteinemia (HLP) and thrombophilia, in relation to atherosclerosis incidence and progress in these patients.

A high incidence (57.90%) of the cases with thrombophilia was underlined in the elderly with HLP (a phenomenon obvious especially in the 70-year-old elderly), as well as the significantly increased frequency of thrombophilic factors in the mixt HLP of the type IIb.

The significant prevalence of females (77.9%) in the elderly sample with dyslipidemia is in contrast with the significantly higher frequency of thrombophilia in men (71.47% as compared to 53.80% in women). This is in full agreement with the increase of vascular accidents incidence in the male elderly.

Pointing out an increased incidence (75.10%) of clinically advanced atherosclerosis in the studied sample, the research did not underline significant correlations between the type of HLP on the one hand, and the incidence and the clinically predominant localisation of the disease, on the other hand.

HLP and thrombophilia are discussed in terms of risk factors involved in the evolution and complications of atherosclerotic lesions, with regard to advanced ages too.

BIBLIOGRAPHIE

1. P. BERTHAUX, G. DENKBERG, *Evolution de l'athérosclérose chez les sujets âgés. Certaines lésions sont-elles réversibles?* In: *Progrès en Gérontologie* par François Bourlière. Ed. Médicales Flammarion, Paris, 1969, p. 286—302.
2. S. BERTELSEN, *Problems concerning the definition and grading of aortic atherosclerosis.* Acta path. microbiol. scand., **61,** 1964, 249—260.
3. P. CONSTANTINIDES, *Importance de l'endothélium et des plaquettes sanguines dans la pathogénie de l'athérosclérose.* Triangle, **15,** *2—3,* 1976, 53—61.
4. G. A. GRESHAM, *L'athérosclérose, ses causes et sa réversibilité potentielle.* Triangle, **15,** *2—3,* 1976, 39—43.
5. R. ROSS, *Rôle dans l'athérosclérose, du traumatisme endothélial, de la prolifération musculaire lisse et des facteurs plaquettaires.* Triangle, **15,** *2—3,* 1976, 45—51.
6. G. SCHLIERF, *L'athérosclérose peut-elle régresser chez l'homme?* Triangle, **15,** *2—3,* 1976, 71—76.
7. Y. STEIN, O. STEIN, *Mobilisation du cholestérol de cellules isolées et en culture de tissu.* Triangle, **15,** *2—3,* 1976, 63—70.
8. A. ASLAN, Symposium « Biothrophic Therapy in Geriatrics », Bucarest, le 29 déc. 1970.
9. A. ASLAN, G. ENĂCHESCU, *Modifications du syndrome humoral chez les athéroscléreux âgés, sous l'influence du traitement biotrophique à l'Aslavital.* Romanian J. Geront. Geriatrics, *1,* 1980, 73—81.
10. J. L. BEAUMONT, L. A. CARLSON, G. R. COOPER, Z. FEIFAR, D. S. FREDRICKSON, T. STRASSE, *Classification of hyperlipidemias and hyperlipoproteinemias.* Bull. Wld Hlth Org., **43,** 1970, 891.
11. D. M. SPAIN, V. A. BRADESS, *Relationship of coronary thrombosis to coronary atherosclerosis and ischemic heart disease.* Amer. J. Med. Sci., **240,** 1960, 701—710.
12. P. EILERSEN, M. FABER, *The human aorta. VI. The regression of atherosclerosis in pulmonary tuberculosis.* Arch. Path., **70,** 1960, 117—121.
13. S. GLAGOV, D. A. ROWLEY, R. J. KOHUT, *Atherosclerosis of human aorta and its coronary and renal arteritis.* Arch. Path., **72,** 1961, 558—571.
14. G. F. FALCONER, C. W. M. ADAMS, *Relationship between nutritional state and severity of atherosclerosis.* Guy's Hosp. Rep., **114,** 1965, 130—139.
15. R. W. WISSLER, *Atherosclerosis; Can it regress? Proceedings of a Symposium, Wiesbaden, 1975.*
16. N. G. ARDLIE, R. L. KINLOUGH, C. J. SCHWARTZ, *In vivo thrombosis and platelet aggregation in myocardial infarction.* Brit. Med. J., *1,* 1966, 888.
17. G. A. BOUVIER, P. ROSNER, S. BERTHAUD, J. RITSCHARD, J. R. SCHERRER, E. HAUSER, *Anomalies du comportement plaquettaire lors d'infarctus du myocarde.* Cardiologia, **50,** 1967, 232.
18. J. R. O'BRIEN, J. B. HEYWOOD, J. A. HEADY, *The quantitation of platelet aggregation induced by four compounds: a study in relation to myocardial infarction.* Thromb. Diath. haemorrh., **16,** 1966, 752.
19. K. BREDDIN, *Experimental and clinical investigations on the adhesion and aggregation of human platelets.* Exp. Biol. Med., *3,* 1968, 14.
20. R. C. HARTMANN, *Tests of platelet adhesiveness and their clinical significance.* Semin. Haemat., *5,* 1968, 60.
21. J. R. HAMPTON, J. R. A. MITCHELL, *A transferable factor causing abnormal platelet behaviour in vascular disease.* Lancet, *2,* 1966, 764.

22. A. G. BECKETT, J. G. LEWIS, *Mobilization and utilization of body fat as an aetiological factor in occlusive vascular disease in diabetes mellitus.* Lancet, *2*, 1960, 14.
23. R. D. BUNAG, C. R. DOUGGLAS, S. INAI, R. M. BERNE, *Influence of pyrimido-pyrimidine derivative on deamination of adenosine by blood.* Circulat. Res., **15,** 1964, 83.
24. J. CORVILAIN, A. CHAMPENOIS, H. LOEB, M. ABRAMOV, *Effect of fasting on level of plasma non-esterified fatty acids in normal children, normal adults and obese adults.* Lancet, *1*, 1961, 534.
25. J. W. KERR, I. MAC AULAY, R. PIRRIE, *Platelet aggregation by phospholipids and free fatty acids.* Lancet, *1*, 1965, 1296.
26. R. FARBISZEWSKI, Z. SKYZYDLEWSKI, K. WOROWSKI, *The effect of lipoprotein fractions on adhesiveness and aggregation of blood platelets.* Thromb. Diath. haemorrh., **21,** 1969, 89.
27. G. GAETANO, J. VERMYLEN, M. VERSTRAETE, *L'inhibition de l'agrégation plaquettaire: données expérimentales et perspectives cliniques.* Nouv. Rev. franç. Hémat., **XI,** *3*, 1971, 339—364.
28. R. M. HARDISTY, R. A. HUTON, *Platelet aggregation and the availability of platelet factor 3.* Brit. J. Haematol., **12,** 1966, 764.
29. J. E. FRENCH, In: *International Review of Experimental Pathology.* Eds. G. W. Richter, M. A. Epstein, Academic Press, New York — London, 1966, p. 253.
30. T. D. STEVENSON, G. R. SCHRODT, L. M. REED, *Coagulant properties of normal and arteriosclerotic aortas.* Amer. J. Med. Sci., **241,** 1961, 632—636.
31. J. L. BEAUMONT, *Les facteurs de risque et la pathogénie de l'athérosclérose.* Triangle, **14,** *1*, 1975, 9—16.

ROMANIAN J. GERONT. GERIATRICS, 1981, 2, 1, p. 85–94

THE EFFECT OF GEROVITAL H_3 TREATMENT ON PLASMA STEROIDS IN ELDERLY SUBJECTS [1]

DENISE DRAFTA*, D. STANESCHI**, EMILIA STROE*, A. E. SCHINDLER***, CĂTĂLINA LÖSNER **

*Institute of Endocrinology, Bucharest, Romania
** The National Institute of Gerontology and Geriatrics, Bucharest, Romania
*** Universitätsfrauenklinik, Tübingen, F. R. of Germany

Summary. Gerovital H_3 (GH_3) was administered to 24 healthy ambulatory volunteers aged 50 to 79 years in four repeated series of 12 intramuscular injections according to the following schedule: in the 1st and 2nd series, one ampoule daily with a ten-day interval between the first and the second series; in the 3rd and 4th series, one ampoule three times a week for four weeks, with a two-month break between the 2nd, 3rd and 4th series. The most important hormonal changes recorded after GH_3 treatment were: a) the first two series of intensive GH_3 treatment induced an increase in plasma cortisol ($p < 0.001$) followed after the 4th series, at approximately seven months after the initiation of the treatment, by a fall of cortisol and 17-hydroxyprogesterone levels; b) the post-treatment changes of plasma estrone levels in elderly women seem to suggest a "moderating" effect of the GH_3 treatment on estrone production; c) no significant changes of plasma testosterone and DHT were noted in elderly men after the GH_3 treatment. A second group investigated in the present study, consisting of 14 ambulatory, chronically GH_3-treated subjects, presented normal values of cortisol, 17-OH-P, estrone and estradiol after long-term GH_3 treatment.

Very few studies on the endocrine effects of Gerovital H_3 treatment are available [1, 2]. A number of authors have already drawn attention to the MAO-inhibition effect of Procaine (Gerovital H_3) [3, 4] with a consequent effect on catecholamine levels [5]. This study reports the plasma steroid changes in 24 healthy ambulatory volunteers, following an intensive Gerovital H_3 (GH_3) treatment, and in 14 ambulatory, chronically GH_3-treated elderly subjects.

SUBJECTS AND METHODS

The first group of elderly subjects consisted of twenty-four healthy ambulatory volunteers (14 women and 10 men) aged 50 to 79 years, treated in the Central Geriatric Policlinic of Bucharest.

The second group investigated consisted of 13 ambulatory, chronically GH_3-treated subjects (9 women and 4 men) aged 70 to 80 years.

Control subjects. Plasma steroid values in the second group were compared with those found in 40 control subjects (22 women and 18 men) aged 50 to 70 years.

The control subjects and the elderly subjects treated with Gerovital H_3 were carefully selected from a large group, to exclude any history of major chronic disease or major endocrine disease; an enlarged prostate was another reason for exclusion from this study, as were patients on tranquillizers and antihypertensive therapy.

[1] With the expert technical assistance of Melania Busneanu and Mihaela Rotaru-Buda.
Reprint requests should be addressed to: Denise Drafta M.D., Institute of Endocrinology, 34, Bd. Aviatorilor, R-71279-Bucharest, Romania.

Gerovital H_3 treatment was given to the first group of elderly subjects in four repeated series of 12 intramuscular injections according to the following schedule: in the 1st and 2nd series one ampoule daily with a ten-day interval between the 1st and 2nd series; in the 3rd and 4th series, one ampoule was given three times a week for four weeks with a two-month break between the 2nd, the 3rd and the 4th series (Fig. 1).

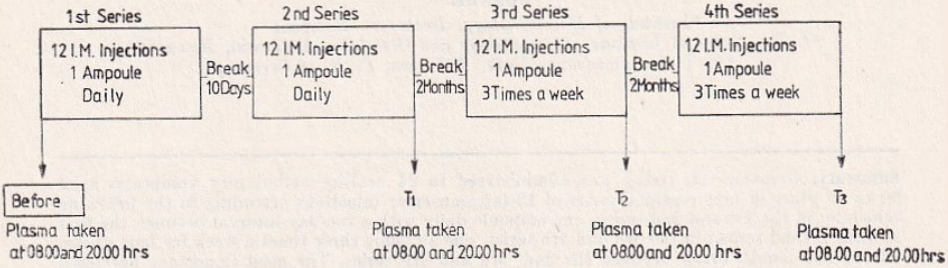


Fig. 1. — Schedule of the Gerovital H_3 treatment.

In the second group, a long-term Gerovital H_3 treatment was given from 1952 to 1977 in oral and intramuscular administration, according to the schedules of the National Institute of Gerontology and Geriatrics, Bucharest: series of 12 shots (3 per week), with a 4-month break between the series.

Plasma steroid determinations. In the first group, cortisol, estrone (E_1), estradiol (E_2), 17-hydroxyprogesterone (17-OH-P), progesterone, testosterone and dihydrotestosterone (DHT) were determined by RIA in duplicate, in plasma samples obtained at 08.00 and 20.00 hrs, before the treatment and then after the 2nd (T_1), 3rd (T_2) and 4th (T_3) series of Gerovital H_3 (Fig. 1). In the second group, cortisol, 17-hydroxyprogesterone, estrone and estradiol were measured by RIA in duplicate, in plasma samples obtained at 08.00 and 20.00 hrs, after a long-term Gerovital H_3 treatment.

In all elderly subjects, blood was obtained in cooled heparinized tubes and plasma was immediately separated by centrifugation at 4 c and stored deep-frozen until assayed. The plasma steroid methods used in this study have been recently summarized by us [6]. Cortisol was assayed by RIA using antiserum against cortisol-21-succinyl-BSA (Cortisol [^{3}H]-RIA-PAK-NEN-F.R. of Germany). Estrone and estradiol were separated on Sephadex LH-20 columns (Benzene-methanol, 85 : 15, v/v) according to the methods of Castanier and Scholler [7] and Verdonck and Vermeulen [8], and assayed by RIA using antiserum against estradiol-17β-succinyl-BSA (Estrone/estradiol [^{3}H]-RIA-PAK-NEN-F.R. of Germany). 17-hydroxyprogesterone and progesterone were separated on Sephadex LH-20 columns (Benzene-methanol, 95 : 5, v/v) and determined by RIA using for 17-OH-P antiserum ROB M 86 against 11-desoxycortisol-21-monosuccinate-BSA from W. Butt, Birmingham-England, and for progesterone, antiserum against progesterone-11-hemisuccinate-BSA (Progesterone [^{3}H]-RIA-KIT-CEA-France). Testosterone and dihydrotestosterone (DHT) were separated on Sephadex LH-20 columns (isooctane: benzene-methanol, 90:5:5, v:v:v) and determined by RIA using antiserum against testosterone-3-oxime-BSA (Testosterone [^{3}H]-RIA-PAK-NEN-F.R. of Germany).

Student's "t" test was used for all statistical analyses.

RESULTS

In the 1st group of subjects the intensive Gerovital H_3 treatment, consisting of the first two series of injections, induced 24 hours after the 2nd series (T_1) a

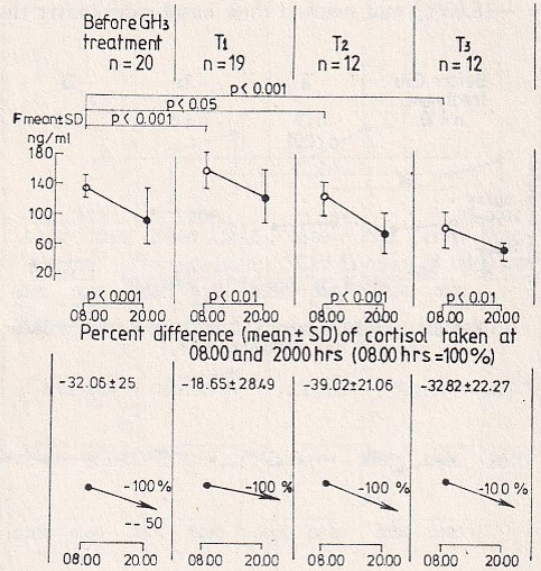


Fig. 2. — The effect of GH_3 treatment on plasma cortisol in elderly people.

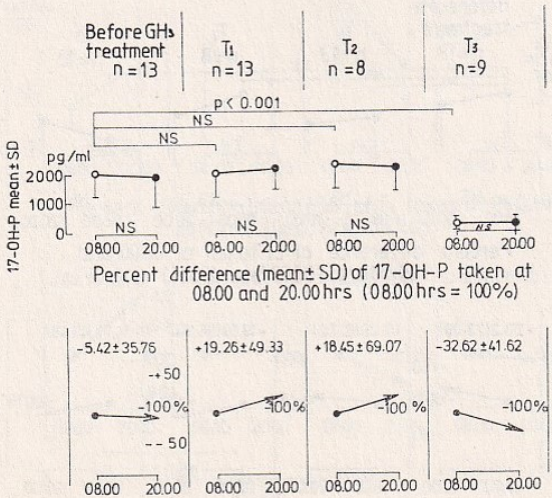


Fig. 3. — The effect of GH_3 treatment on plasma 17-OH-P in elderly women.

significant increase of morning and evening cortisol values ($p < 0.001$), followed, after the 4th series (T_3), by a fall of cortisol (Fig. 2) and 17-OH-P levels (Figs 3 and 4). The percent differences of cortisol values in plasma samples taken at 08.00 and 20.00 hrs (−32.06%) were reduced by intensive Gerovital H_3 treatment (T_1 = = −18.65%) and reached their basal values after the 3rd (T_2) and 4th series (T_3).

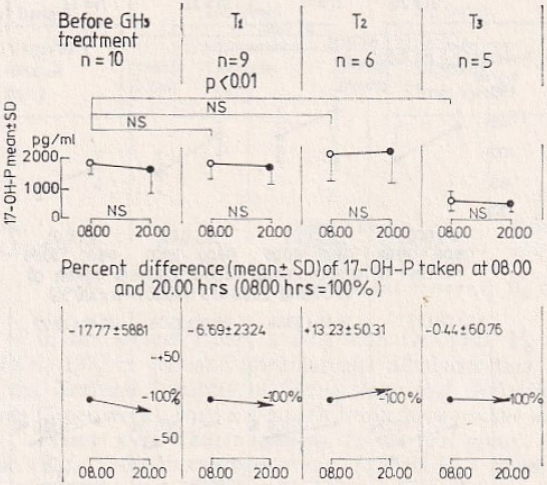


Fig. 4. — The effect of GH_3 treatment on plasma 17-OH-Pin elderly men.

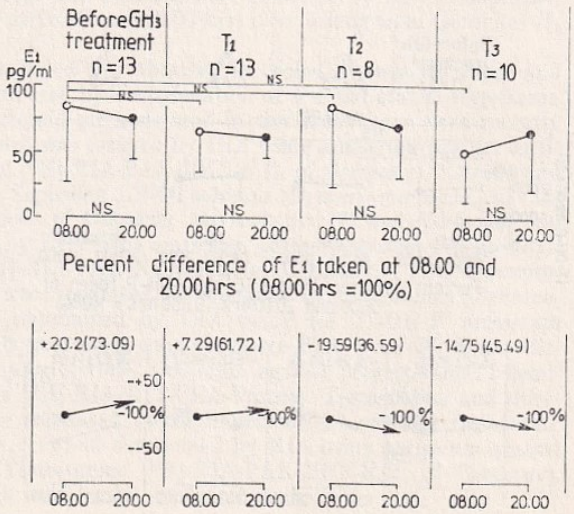


Fig. 5. — The effect of GH_3 treatment on plasma estrone in elderly women.

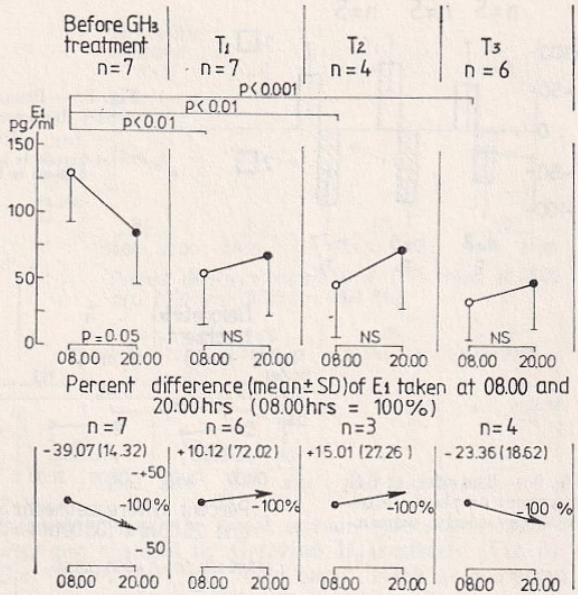


Fig. 6. — The effect of GH_3 treatment on high basal estrone levels in elderly women.

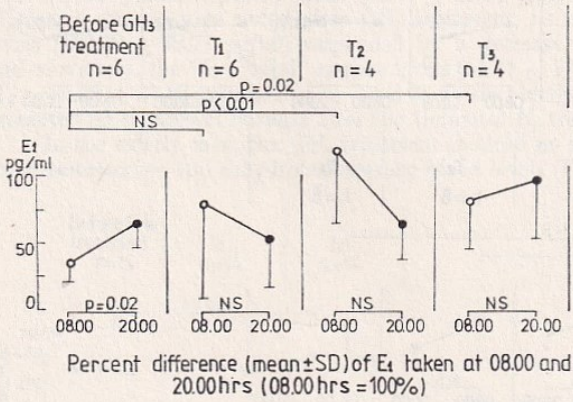


Fig. 7. — The effect of GH_3 treatment on low basal estrone levels in elderly women.

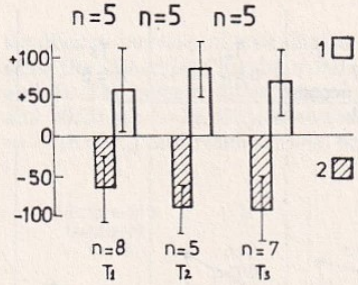


Fig. 8. — Plasma estrone differences (mean ±SD) between the basal and post-GH_3 treatment levels.

1, Percent increase in low basal estrone levels; *2*, percent decrease in high basal estrone levels.

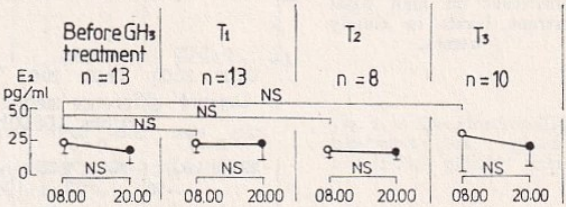
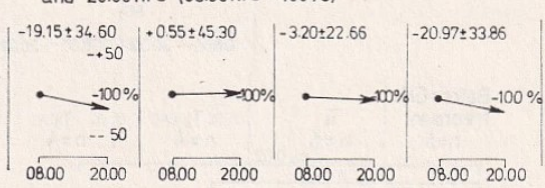


Fig. 9. — The effect of GH_3 treatment on plasma estradiol in elderly women.



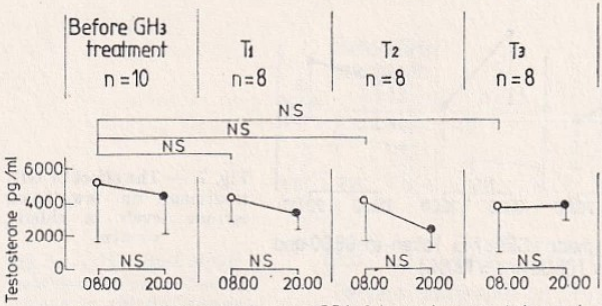
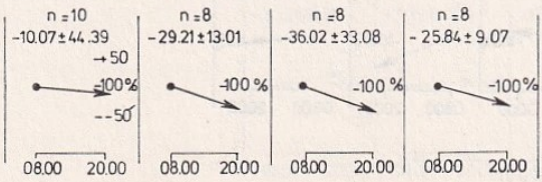


Fig. 10. — The effect of GH_3 treatment on plasma testosterone in elderly men.



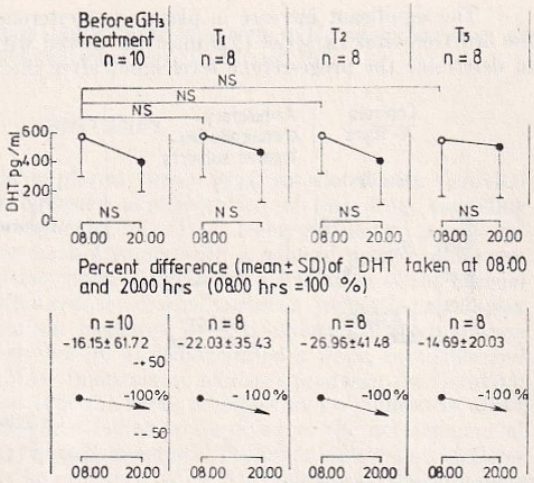


Fig. 11. — The effect of GH_3 treatment on plasma DHT in elderly men.

In the elderly GH_3-treated women, the basal estrone values presented a wide-range variation and were not changed by Gerovital H_3 treatment (Fig. 5); if we consider separately the "high basal" and "low basal" levels as compared with normal postmenopausal mean (61.78 $\pm$ 26.94 pg/ml) [6], significant changes of plasma estrone were noted after GH_3 treatment, i.e. the "high basal" estrone levels (130.32 $\pm$ 38.77 pg/ml) responded by a decrease (T_3 = 32.08 $\pm$ 30 pg/ml) and conversely, the "low basal" estrone levels (34.21 + 17.27 pg/ml) by an increase (T_3 = 82.08 + 37.88 pg/ml) (Figs 6, 7 and 8). In the elderly women, plasma estradiol presented no significant changes after the Gerovital H_3 treatment (Fig. 9).

In the elderly men, the GH_3 treatment induced no significant change in the mean testosterone and dihydrotestosterone blood levels (Figs 10 and 11).

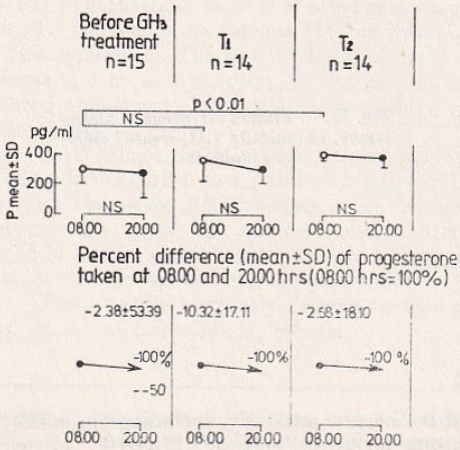


Fig. 12. — The effect of GH_3 treatment on plasma progesterone in elderly subjects.

The significant increase in plasma progesterone noted in elderly people after the 3rd Gerovital H_3 series (T_2) must be viewed with caution as we were not able to determine the progesterone level later, after the 4th series (T_3) (Fig. 12).

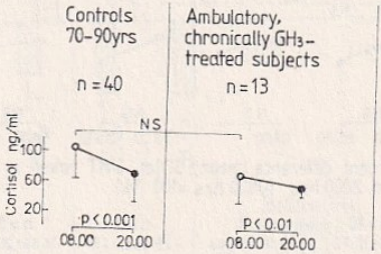
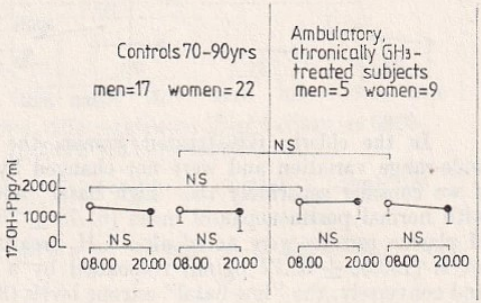


Fig. 13. — Plasma cortisol in ambulatory, chronically GH_3-treated elderly subjects.

Fig. 14.—Plasma 17-OH-P in ambulatory, chronically GH_3-treated elderly subjects.



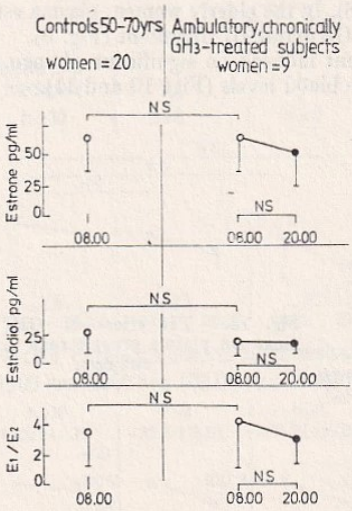


Fig. 15. — Plasma estrogens in ambulatory, chronically GH_3-treated elderly subjects.

In the second group investigated in the present study, including chronically GH_3-treated elderly subjects, the plasma levels of cortisol, 17-OH-P, estrone

and estradiol were within normal limits after long-term GH_3 administration, as compared with their age-matched controls (Figs 13, 14 and 15).

DISCUSSION

The most important change in plasma steroid levels associated with Gerovital H_3 therapy, was noticed after intensive administration of this drug, consisting of the first two series of 12 intramuscular injections, 1 ampoule daily, namely the increase of morning and evening cortisol values with a reduced percent difference between them. These findings demonstrate a significant stimulation of the adrenal cortex by the GH_3 treatment with a reduced diurnal variation, suggesting a complex neuro-hormonal feedback mechanism mediated by GH_3-induced MAO inhibition in the hypothalamus. Previous studies [3, 4] demonstrated a weak, reversible and fully competitive inhibition of MAO (monoamine oxidase) produced by Gerovital H_3. A series of studies [9] suggest that the aging processes may significantly affect monoamine mechanisms and may be a factor predisposing to the development of disorders of the central nervous system homeostasis. The favourable action of Gerovital H_3 on the aging process may be explained by its MAO inhibition effect (increase in the neurotransmitters content).

Our present data demonstrate that stimulation of the adrenal function by the intensive Gerovital H_3 treatment, was followed approximately seven months after the initiation of therapy by diminished adrenal activity. Mention should be made that Gordon et al. [1, 2] reported decreased urinary levels of 17-ketosteroids after a six-month Gerovital H_3 treatment (EP = European Procaine), administered also by repeated cycles, but according to a different procedure.

The beneficial effects of Gerovital H_3 treatment on patients suffering from collagen disease and other forms of arthritis [10] might be also due to the increased amounts of cortisol induced by this treatment.

The effect of Gerovital H_3 treatment on plasma estrone level suggests a "moderating" effect of the treatment on the estrone production which may also be mediated by the hypothalamic control of adrenal androgens secretion as precursors in extragonadal conversion to estrone [11] or directly by interfering with the efficiency of this conversion. The rate of this conversion is markedly altered by obesity, liver disease and hyperthyroidism. In our present study we did not find in the elderly treated women any correlation between high estrone levels and the excess of adipose tissue.

In conclusion, the plasma steroid profile revealed a significant stimulation of the adrenal cortex as a result of 2 series of i.m. daily shots, with a 10-day break between the series. After 2 more series (3 shots per week) with a 2-month break between the series, the adrenal activity decreased. The post-treatment changes noted in plasma estrone of the elderly women suggest a "moderating" effect of the GH_3 treatment on the estrone production.

These results obviously deserve further exploration to determine the nature and extent of Gerovital H_3 effects.

Résumé. 24 volontaires sains du point de vue clinique et ayant l'âge de 50—79 ans ont fait un traitement ambulatoire au Gérovital H_3, qui a consisté en 4 séries, à raison de 12 injections i.m. conformément au schéma suivant: pendant la première et la deuxième série une ampoule chaque

jour, avec une pause de 10 jours entre les séries; pendant la troisième et la quatrième série une ampoule 3 fois par semaine pendant 4 semaines, avec une pause de 2 mois entre les 2 séries. Les plus importantes modifications hormonales enregistrées à la suite du traitement au Gérovital H_3 ont été les suivantes: a) les 2 premières séries de traitement intensif ont provoqué une augmentation du cortisole plasmatique ($p < 0{,}001$) suivie après la 4e série (7 mois approximativement après le début du traitement) par une diminution du cortisol et de la 17-hydroxyprogestérone; b) chez les femmes âgées, la modification du niveau de l'estrone plasmatique après le traitement semble suggérer un effet « modérateur » du traitement au Gérovital H_3 sur la production de l'estrone; c) on n'a observé aucune modification significative de la testostérone et de la DHT chez les hommes âgés traités au Gérovital H_3; d) un 2e groupe étudié a inclus 14 sujets soumis à un traitement ambulatoire de longue durée au Gérovital H_3; après ce traitement les sujets ont présenté des valeurs normales du cortisol, de la 17-OH-P, de l'estrone et de l'estradiol.

REFERENCES

1. A. ABRAMS, T. SHELDON, P. GORDON, C. PECHTEL, A. HILKEVITCH, *The effects of a European Procain preparation in an aged population. I. Psychological effects.* J. Geront., **20,** *2*, 1965, 139—143.
2. P. GORDON, J. FUDEMA, G. L. SNIDER, A. ABRAMS, S. TOBIN, J. KRAUS, *The effects of a European Procain preparation in an aged population. II. Physiological effects.* J. Geront., **20,** *2*, 1965, 144—150.
3. S. KENT, *A look at Gerovital, the "youth" drug.* Geriatrics, Dec. 1976, 95.
4. M. D. Mac FARLANE, H. BESBRIS, *Procain (Gerovital H_3) therapy: Mechanism of inhibition of monoamine oxidase.* J. amer. Geriat. Soc., **22,** *8*, 1974, 365—371.
5. T. SAFIRESCU, M. BÎRSAN, A. CHIRA, L. HARTIA, D. STANESCHI, C. VASCAN, T. IONESCU, E. PĂUȘESCU, R. CHIRVASIE, *Variations of catecholamine and catecholaminuria under the influence of Gerovital H_3 treatment.* Abstracts of the 8th European Congress of Clinical Gerontology, Neptun, Romania, 7—10 September 1977, p. 102.
6. D. DRAFTA, A. E. SCHINDLER, ST. M. MILCU, E. KELLER, E. STROE, E. HORODNICEANU, I. BĂLĂNESCU, *Plasma hormones in pre- and postmenopausal breast cancer.* J. Steroid Biochem., **13,** 1980, 793—802.
7. M. CASTANIER, L. SCHOLLER, *Dosage radioimmunologique de l'estrone et de l'estradiol-17β-plasmatique.* C.R. hebd. Séances Acad. Sci., Paris, **271,** série D, 1970, 1787—1789.
8. L. VERDONCK, A. VERMEULEN, *Comparison of quick methods for the estimation of estradiol in plasma by RIA.* J. Steroid Biochem., **5,** 1974, 471—479.
9. D. S. ROBINSON, *Changes in monoamine oxidase and neuroamines with human development and aging.* Fed. Proc., **34,** *1*, 1975, 103—107.
10. I. BULBUC et al., *Gerovital H_3 therapy in the chronic degenerative rheumatism.* Abstracts of the 8th European Congress of Clinical Gerontology, Neptun, Romania, 7—10 September 1977, p. 35.
11. P. K. SIITERI, P. C. Mac DONALD, *Role of extraglandular estrogen in human endocrinology.* In: *Handbook of Physiology* (edited by R. O. GREEP and E. ASTWOOD, Section 7: Endocrinology, vol. II. *Female Reproductive System*, Part I. Am. physiol. Soc., Washington, 1973, pp. 615—629.

ROMANIAN J. GERONT. GERIATRICS, 1981, 2, 1, p. 95–104

ANTIDEPRESSIVE EFFECTS OF GEROVITAL H_3 PROPHYLACTIC TREATMENT

I. CERNEA, VICTORIA NEGOESCU-BODOR

The National Institute of Gerontology and Geriatrics
Bucharest, Romania

Summary. The present study investigated the antidepressive effects of a long-term (3 years) treatment with Gerovital H_3 on a lot of 50 subjects, aged 45 to 60, employed in a heavy industry unit. This lot, submitted to a prophylactic treatment with Gerovital H_3 scored lower statistically significant values with the Zung Self-Rating Depression Scale and Woodworth Inventory, as compared to a control sample of the same size and profession. The study pointed out that the antidepressive action of the treatment did not involve only somatic symptoms, but also cognitive and affective ones, demonstrating the complex antidepressive action of Gerovital H_3. Knowing the role played by age in the etiology of depression, we could observe its influence on the depressive states of treated and untreated subjects. Although it proved to be an independent variable, that accounted for a part of the variance, the treatment also brought about significant changes in the results obtained in the treated subjects.

1. Of the multiple disturbances that accompany aging, depression is one of the most intense and tends to increase with age [1]. As reported in literature, depression is the most common emotional disorder or the most common psychiatric symptom found in the elderly [2]. The depressive state can be often identified after two basal behaviours: lack of interpersonal communication and of interest in the surrounding environment. Unlike the young, the elderly often find means of concealing their depression using a variety of mechanisms; they often deny depression states and express their depressive symptoms by somatic and hypochondriac manifestations. Hence, the difficulty in diagnosing and promptly treating the depression.

1.1. The biological factors play an important role in the etiology of depression in the aged. Of them, mention should be made of the increased monoamine oxidase activity in plasma and rhombencephalon platelets, REM sleep deprivation and hormonal changes induced by the decreased responsiveness of the pituitary gland and hypothalamus; the conjugated action of these factors results in increased vulnerability to stress [3]. In spite of this, the idea that depression is only determined by biological, physiological or genetic factors is obsolete. It is unanimously admitted that psychological or environmental factors play an important role in the etiology of depression. Depression is often the result of self-esteem progressive diminution. This phenomenon is due to certain circumstances such as the gradual loss of friends and family, a decrease in memory and other intellectual abilities, the absence of socio-professional status. In close relation with self-esteem loss is the feeling of being neglected, followed by a sense of uselessness. All these circumstances are usually associated with physical illness. In short, in a life period when stress

becomes hard to tolerate the elderly are subjected to several changes in their internal and external environment and must cope with multiple and progressive losses. The role of culture is decisive in overcoming critical situations and finding alternative adjusting behaviours. Yet, it seems that culture is a variable which does not affect depression's symptomatology, but contributes to overcoming the stress that produces depression.

1.2. Depression is defined operationally by the following features: a) Disorders in the state of mind characterized by acute feelings of discouragement, sadness, tears; b) Physiological symptoms that include daily variations, sleep disturbances, loss of appetite, of libido, and of weight, constipation, tachycardia and inexplicable fatigue; c) Psychomotor disturbances, either of delay or of excitement; d) Mental disorders including confusion, despair, hesitation, irritability, dissatisfaction, self-depreciation, a feeling of emptiness, suicide thoughts [4].

Although most of the studies based on the inventory of depressive symptoms in populations of different age conclude that depressive symptomatology is more obvious in subjects aged over 65 [5], other authors such as Nielsen [6], Sorensen and Stromgren [7] find that the highest rate of depression occurs between 25 and 65 years of age. Gurland [8] maintains that this situation is explained by the fact that the aged display temporary yet recurrent depressive states, which are difficult to diagnose as such, whereas Zemore and Eames [9] consider that a more plausible hypothesis of the different opinions in literature is that any control inventory on depression includes various symptoms of somatic diseases. In a comparative study on the aged and young adults, these authors found that the two groups differ only as far as the somatic symptoms of depression are concerned (the aged present more numerous somatic symptoms) and do not vary as regards cognitive and affective ones, which leads to the conclusion that somatic symptoms might be rather explained by normal psychological changes accompanying aging than by a higher depression rate among the aged. Somatic symptoms might be indicators of depression only for the young adults, whereas for the aged they might represent a worse health condition. Other authors consider somatic symptoms as being part of the clinical picture of depression, even when they occur in isolation (with no obvious psychical phenomena, as in hidden depressions) [10].

1.3. Starting from these contradictory data we were interested in the study of depression in subjects aged 45 to 60, employed in a heavy industry unit, of which some were submitted to a prophylactic treatment with Gerovital H_3. The prophylactic treatment with Gerovital H_3 was included in a larger action of aging prophylaxis initiated by the National Institute of Gerontology and Geriatrics on a national scale by creating some gerontological points in the big industrial units of Romania.

The antidepressive effects of Gerovital H_3 were pointed out by Prof. Dr. Ana Aslan in a paper entitled "A New Method for the Prophylaxis and Treatment of Aging with Novocain; Eutrophic and Rejuvenating Effects", that pointed out the positive results obtained at the Institute of Geriatrics in Bucharest between 1951 and 1954 [11, 12, 13].

Worth mentioning are Zung and Wang's studies [14] on the antidepressive effects of Gerovital in comparison with those of Imipramin and Placebo. Although both the Gerovital H_3 group and the Imipramin group displayed ameliorations, only the Gerovital H_3 group recorded statistically significant differences in the global clinical evaluation of depression prior to and after treatment. Also, only

in the Gerovital H_3 group was a significant difference obtained between the anxiety self-rating scores before and after treatment. Several studies based on the global clinical method and various depression scales (Zung, Hamilton, Beck), reported the positive effects of Gerovital H_3 in the treatment of depression in the elderly population.

The pharmacological basis of the Gerovital H_3 antidepressive action by its influence on the level of cerebral monoamines was also elucidated.

Our study aimed at finding out whether Gerovital H_3 action involves both the somatic and the cognitive and affective symptoms of depression, or whether the scores of self-rating depression scales obtained in the treated lots are lower due to the fact that the treatment reduces only the somatic symptomatology of depression.

2. MATERIAL AND METHOD

2.1. *Subjects.* The research was conducted on a lot of 50 skilled workers aged 45 to 60, employed in a heavy industry unit, subjected to a three-year prophylactic treatment with Gerovital H_3, and on a control group, similar in point of education, size and work facilities. All the subjects displayed a relatively homogeneous educational and cultural level. The mean age of the treated lot was 52.44 (standard deviation 3.53), and of the control lot 52.30 (standard deviation 4.05).

2.2. *Experimental procedure.* All the subjects were applied:

a) Zung Self-Rating Depression Scale (1974). As described by its author himself, this method was created starting from the clinical diagnosis criteria most often used to characterize depressive diseases, that is a permanent state of depression accompanied by concomitant physiological and psychological disturbances [15].

b) The Woodworth Inventory for the discovery of the pathological tendencies concerning affectivity, emotional instability, schizoid, paranoid, and antisocial tendencies, etc.

c) An original inventory that investigates self-perception of psychical and physical health state and the self-image related to aging.

3. RESULTS AND DISCUSSION

3.1. Comparing the compound scores obtained by Zung Self-Rating Depression Scale we found that the treated lot registered a lower mean of depression scores ($\bar{x}_1 = 48$) in comparison with that of the control lot ($\bar{x}_2 = 55.3$) for a significance threshold of $p < .01$ (Table 1).

Table 1

Mean of scores obtained with the Zung Self-Rating Depression Scale (N = 100)

	$\bar{x}$	s.d.	t	p
Treated lot	48	11.9	2.64	<.01
Untreated lot	55.3	15.4		

On peut considérer cette date comme le moment qui marque le début de la période scientifique de la gérontologie, dans notre pays.

Il est vrai que Marinescu a abordé le problème de l'involution neuronale dans un autre travail publié en 1899 dans le n° 20 de la « Revue Neurologique »: *Études sur l'évolution et l'involution de la cellule nerveuse*. Mais le problème n'a pas été traité d'un point de vue gérontologique.

Les idées comprises dans ces travaux ont été reprises et développées dans un article intitulé *Études sur le mécanisme de la sénilité* publié le 30 décembre 1904 dans le n° 24 de la « Revue Générale des Sciences pures et appliquées ».

Les données de cet article sont fondées sur des observations microscopiques des préparations de tissu nerveux, colorées par la méthode Nissl ou imprégnées à l'argent par la méthode Cajal.

L'objectif poursuivi a été de déchiffrer les altérations morphologiques des neurones et des réactions névralgiques qui se produisent lors de la sénescence. Afin de les comprendre, il a comparé les aspects de la sénescence du tissu nerveux aux aspects histopathologiques du même tissu, provoqués par des intoxications (à la toxine botulinique), infections virales (la rage) après les nécroses (dues aux micro-embolies avec poudre de licopodium), après l'hypertermie, l'hypoxie, etc. Aujourd'hui même, 80 ans après, les descriptions de Marinescu ont une précision impressionnante et ses interprétations ont une élégance remarquable. On lit avec émotion les feuilles jaunies de la revue et on constate que les données exposées sont encore valables.

Ainsi Marinescu décrit dans le tissu nerveux vieilli: la diminution en volume des neurones, la diminution de la substance chromatophile de Nissl, les altérations de la membrane nucléaire, la division et la disparition du nucléole.

Très importante est son analyse sur la sénescence de l'appareil neurofibrilaire. Certaines neurofibrilles se maintiennent normales, d'autres se dissipent et disparaissent, enfin d'autres s'hypertrophient et acquièrent une couleur intense par le nitrate d'argent. Plus tard Marinescu d'occupera du destin morphologique des neurofibrilles dans les cas de vieillissement pathologique (par exemple: les démences abiotrophiques, préséniles et séniles).

Dès ses premiers travaux, Marinescu a observé dans les neurones sénescents un processus d'accumulation croissante d'un pigment jaune (la future lipofuscine) et il a deviné l'importance de ce stockage intracytoplasmatique.

Marinescu a décrit aussi les remaniements névrogliques. Il a insisté surtout sur l'agglomération des cellules névrogliques autour des neurones pendant le processus de dégénérescence sénile.

Le fait essentiel est qu'il explique cette « satellitose » comme un phénomène secondaire de l'abiotrophie neuronale, tout en combattant les hypothèses existantes à l'époque respective, conformément auxquelles le phénomène initial du vieillissement nerveux serait une agressivité croissante et anormale de la névroglie contre les neurones. Il prend une attitude ferme vis-à-vis de Metchnikoff qui avait soutenu que la sénescence au niveau du système nerveux est déterminée par une phagocytose progressive des neurones par les macrophages (névroglie). Le rejet de l'hypothèse de la neuronophagie est complété par Marinescu par une autre hypothèse concernant les causes des réactions gliales de la sénescence. Celles-ci seraient provoquées par des modifications chimiques suscitées par la dégénérescence neuronale.

Il accepte — avec certaines réserves — l'idée de Weigert concernant la prolifération de la névroglie considérée comme un processus compensatoire, qui équilibre le phénomène de la disparition sénile des neurones. Il faut mentionner que Marinescu a été parmi les premiers à signaler le phénomène de « dépopulation » neuronale.

considéré aujourd'hui comme la caractéristique morphologique primordiale de la sénescence névraxiale. Partant de cette « dépopulation » il explique la neuronophagie, à savoir: « les macrophages nettoient le terrain occupé par les cadavres des cellules et des fibres nerveuses ».

De l'analyse micromorphologique du vieillissement du système nerveux, Marinescu conclut que ce vieillissement est le résultat du processus de dégradation produit dans l'intimité de la cellule nerveuse. Il est possible surtout grâce au caractère postmitotique des neurones, qui ont toujours l'âge de l'organisme auquel ils appartiennent.

Les idées présentées ci-dessus ont été reprises sous une forme définitive dans l'une des plus importantes monographies concernant la morphologie du système nerveux: *La cellule nerveuse* parue en 1909 à Paris, où Marinescu consacre à la sénescence neuronale un chapitre entier.

Intrigué par les aspects morphologiques de la sénescence neuronale et convaincu du fait que les éléments qui la déterminent doivent être recherchés à un niveau sous-cellulaire, le savant roumain a étudié ce problème qu'il s'est efforcé d'approfondir et de comprendre dans le contexte du niveau technique et théorique des sciences à l'époque respective. Quoique la biologie moléculaire ne fût pas encore bien précisée, Marinescu avait considéré le processus de sénescence comme un phénomène physique et chimique. Etant donné qu'à cette époque la biologie cellulaire était dominée par les résultats des recherches concernant les solutions colloïdales, Marinescu a formulé l'hypothèse remarquable selon laquelle le substratum de la sénescence est une altération au niveau de la structure colloïdale du protoplasme.

Dans une série d'études publiés en 1912, le prof. Marinescu, en utilisant surtout l'ultramicroscopie, étudie la structure colloïdale des neurones. En extrapolant dans le domaine de la biologie les recherches de Bechold qui avait demontré que les solutions colloïdales se modifient par rapport au temps, il énonce l'hypothèse colloïdale de la sénescence, à savoir: « Nous croyons pouvoir soutenir qu'une théorie de la sénescence qui prend en considération surtout les modifications colloïdales qui se produisent dans toutes les cellules et spécialement dans les cellules du système nerveux par rapport à l'âge correspond aux faits établis par nos recherches, ainsi qu'aux données exactes de la chimie colloïdale en général ». Ce point de vue représente un pas décisif en avant, car il situe le problème de la sénescence et de la mort dans la sphère des phénomènes physiques et chimiques.

Ayant comme point de départ les altérations colloïdales, Marinescu explique l'involution des neurofibrilles sénescentes s'appuyant sur les altérations des colloïdes. Il analyse dans ce sens les modifications décrites par Abzheimer dans les démences séniles ainsi que la formation des corpuscules argentofiles.

En outre, dans un article paru dans « L'encéphale » en 1912, il considère que la formation des plaques séniles est aussi l'expression d'une dégradation colloïdale de l'appareil neuro-fibrillaire. En 1924, il soutient d'une manière catégorique, à la suite de ses propres investigations, que la dégénérescence neuronale du type Abzheimer ainsi que les plaques séniles se retrouvent non seulement dans le cas de la sénescence pathologique mais aussi dans celle normale (ortogère). De cette manière il a contribué essentiellement au perfectionnement du tableau histologique de la sénescence névraxiale normale.

En exposant en 1924 le « mécanisme chimico-colloïdal de la sénilité » Marinescu, se basant exclusivement sur la microscopie optique, a une extraordinaire intuition. En effet, beaucoup avant la découverte des nucléoprotéines, du code et de la programmation génétique, il considère les altérations colloïdales du noyau comme

étant essentielles pour le vieillissement. Du contenu nucléaire « dépend l'évolution de la cellule vers le rajeunissement ou la division, mais aussi vers la sénescence et la mort; en lui, en son constitution chimique, sont inscrites les prédispositions destinées à prédire l'édifice cellulaire, un nouvel essor ou une décrépitude inévitable ». Nous voyons donc que la vision gérontologique de Marinescu préfigure les conceptions modernes informationnelles à l'égard de la sénescence.

Les modifications des solutions colloïdales ne sont pas présentées comme l'unique facteur de la sénescence. C'est pourquoi Marinescu affirme que « la déshydratation progressive, la perte des charges électriques, la désintégration des lipoprotéines, les combustions incomplètes, la modification irréversible des substances colloïdes qui font partie de la structure du protoplasme et du noyau, ainsi que le manque de réintégration ou de synthèse chimique qui ramène l'équilibre exactement à l'état antérieur sont les phénomènes principaux qui se produisent dans toute cellule et sourtout dans la cellule nerveuse et qui catactérisent la sénilité ».

Ainsi qu'on peut voir, le prof. dr. Marinescu décrit clairement le processus du vieillissement cellulaire comme un phénomène très complexe de remaniements biophysique et biochimiques.

Puissamment influencé « par une réflexion profonde de Cl. Bernard », Marinescu a été attiré par l'activité enzymatique endocellulaire. En utilisant des méthodes micro-histochimiques, il a spécialement étudié les systèmes oxydoréducteurs des neurones, en isolant un sous-système catalytique fondé sur le fer et peut-être le manganèse) et un sous-système enzymatique constitué d'oxydases, sous-système relevé par la synthèse du bleu d'indophénole.

Dans deux articles, l'un publié en 1922 dans le volume dédié à S. R. Cajal et l'autre publié en 1924 dans les Annales d'Anatomie pathologique de Paris, Marinescu réunit les résultats de ses observations concernant les oxydases des neurones normaux et pathologiques. Dans ces ouvrages, entre autres, il souligne la diminution progressive des oxydases avec l'âge et admet que la réduction des oxydases du cytoplasme neuronal est parallèle à l'accumulation de pigment jaune (lipofuscine).

Il suit ce phénomène dans le matériel nécropsique mais aussi dans les cultures de tissus (effectuées par la méthode Burrow-Carrel). Marinescu insiste sur le fait que « la diminution graduelle de la quantité d'oxydases et l'apparition des graisses, comme un signe spécifique de la sénescence, se rencontrent dans tous les organes ».

Dans un article publié avec State Drăgănescu en 1923 dans la « Revue Neurologique », il analyse la distribution du fer dans certaines structures névraxiales (globus pallidus, locus niger, le noyau rouge, le noyau denté). De l'analyse des données obtenues par la réaction au sulfure d'ammonium de Guizzeti et celle au bleu de Turnbull, les auteurs concluent que: « les processus pathologiques et la sénilité modifient d'une manière considérable autant la quantité de fer des centres mentionnés en l'augmentant, que la forme sous laquelle il se présente ».

Il résulte donc que, dès le premier quart de ce siècle le prof. Gh. Marinescu, en utilisant uniquement la microscopie a pu préciser qu'à la base du processus de vieillissement se trouvent des phénomènes biochimiques très fins, au niveau desquels les enzymes et les oligoéléments ont un rôle très important.

Ses recherches l'ont porté à la conception que le vieillissement et la mort sont des phénomènes naturels inévitables. Selon son opinion, ils sont des caractéristiques de la matière vivante et font partie — on dirait aujourd'hui — du programme obligatoire de l'existence de tout être vivant.

« La substance vivante s'édifie et s'écroule sans cesse en passant de l'état de matière ordinaire à la « dignité » de matière spécialisée au plus haut degré, pour

déchoir finalement à l'état de mélange d'éléments étrangers », écrivait Marinescu en 1924 dans un chapitre suggestivement intitulé: « La sénescence et la mort sont des phénomènes naturels et nécessaires », faisant partie du travail *Le problème de la sénescence et de la mort naturelle.* Cette conception reflète la position matérialiste qui a été adaptée d'une manière conséquente par le grand savant dans tous ses travaux. Le passage cité a un évident caractère héraclitéen et permet de dégager la manière dialectique selon laquelle il considérait les problèmes de la vie, de la sénescence et de la mort. Dans le mémoire *La sénescence et le rajeunissement*, publié par l'Académie Roumaine en 1929, il cite comme support philosophique de son point de vue Héraclite et Marc Aurèle.

Il est intéressant que Marinescu, dans les conclusions de sa monographie *Le problème de la sénescence et de la mort naturelle* de 1924, inspirée par l'ouvrage de B. Brunhes *La dégradation de l'énergie* publié à Paris en 1908, explique les processus du vieillissement et de la mort en utilisant le concept d'entropie. Il est vrai qu'il n'utilise pas ce terme, mais le texte porte sans ambiguité sur la IIe loi de la thermodynamique. « La sénescence et la mort correspondent à la dégradation de l'énergie vitale qui est fatale parce que la manière des êtres vivants est soumise à une loi générale qui gouverne l'énergie cosmique. C'est une grande et profonde loi naturelle, qui nous permet d'affirmer que le monde matériel s'use et que ses phénomènes deviennent de plus en plus moins caractéristiques ». Dans un langage plus spécialisé, la conclusion finale de Marinescu est que la sénescence et la mort sont des phénomènes naturels dûs à la loi de l'accroissement continu de l'entropie dans les systèmes matériels.

Cette idée apparaît plus clairement dans une autre phrase (1928): « Nous avons constaté par nos recherches d'histochimie une uniformisation d'une manière fatale de la tension de différentes énergies. Ce qui amène la sénescence et la mort ».

Cette conception lui impose une attitude très ferme concernant l'irréversibilité du processus de vieillissement. « Le vieillissement de même que la mort sont des phénomènes naturels et nécessaires; les hypothèses des auteurs qui considèrent le phénomène de la sénilité un accident qui peut être remédié sont en désaccord avec une loi universelle qui gouverne la matière entière ». « À l'état actuel de nos connaissances — le rajeunissement — par n'importe quelle méthode — est une chimère car par malheur, on ne peut pas s'opposer à l'évolution, qui suit son déroulement fatal ».

Tenant compte des données acquises et de la structure conceptuelle à laquelle il était arrivé, Marinescu a abordé critiquement les autres théories contemporaines concernant la sénescence.

C'est ainsi qu'il a combattu avec énergie la théorie phagocytaire et celle de l'autointoxication intestinale de Metchnikoff et ses conclusions pragmatiques (l'utilisation sourtout du sérum cytotoxique, du sérum antileucocytaire et l'extirpation du gros intestin). Il a pourtant exprimé sa profonde admiration pour l'œuvre de Metchnikoff autant dans ses articles polémiques que dans la nécrologie faite à l'Académie Roumaine.

De même, il s'est élevé contre les conceptions de Weissman qui attribuait la sénescence et la mort uniquement à la programmation génétique. Dans la critique qu'il fait, on rencontre de nouveau la vision dialectique de Marinescu. Il considère Weissman trop exclusif et propose un modèle plus élastique où le programme génétique est modulé par les facteurs du milieu.

Il considère incomplète la conception de Parhon et Goldstein qui avaient soutenu en 1919 que la sénescence est due à une distrophie progressive du système

endocrinien. Il invoque comme contre-argument le fait que les plantes (qu'on croyait à l'époque respective comme dépourvues d'hormones) vieillissent aussi, quoiqu'elles n'aient pas de glandes à sécrétion interne.

Il accepte l'existence des dégradations morphologiques et hystochimiques produites avec l'âge dans les glandes endocrines, mais il refuse d'admettre que le « primum movens » de la sénescence se trouve dans ces glandes.

De même, il attire l'attention que si l'on admet la théorie de la distrophie glandulaire, la sénescence « devient une maladie, par conséquent, en principe, susceptible de guérison ». Avec son intransigeance caractéristique il ajoute: « Personne n'a guéri de vieillesse jusqu'à aujourd'hui ».

Aussi combat-il toutes les tentatives de rajeunissement par voie hormonale comme: les injections d'extraits testiculaires (proposées par Brown-Séquard), la ligature et le sectionnement du canal déférent (pratiqué par Steinach), la greffe testiculaire (soutenue par Voronoff), l'injection de sang jeune (soutenue par Javorski), etc.

Mais le pessimisme gérontologique de Marinescu n'est pas quand même absolu. Il ne nie pas totalement la possibilité de pouvoir influencer la sénescence. Dès 1904, il écrivait: « S'il n'est pas possible de rajeunir l'être humain, et d'autant plus de l'empêcher de mourir, la possibilité de prolonger dans certaines conditions, une vie inévitablement passagère ne dépasse pas les pouvoirs humains ». Il admet même que certains moyens de rajeunissement proposés ne sont pas depourvus d'effets.

Ainsi dans une conférence, Marinescu a soutenu la possibilité d'une chimiothérapie du vieillissement. « Le vieillissement est dû à l'absence de synthèses chimiques au niveau des cellules nerveuses . . . C'est pourquoi nous avons recommandé de stimuler la synthèse chimique avec des substances dynamogènes ». On peut donc dire que Marinescu a entrevu les traitements eutrophiques du vieillissement.

Il considère aussi que les traitements appliqués peuvent empêcher l'accélération du vieillissement due à certaines maladies, peuvent retarder la mort et peuvent ainsi prolonger la vie.

En même temps Marinescu a posé le problème de la prophylaxie gérontologique: « L'alimentation, la manière de vivre, le logement ainsi que d'autres facteurs ont une grande influence sur la longévité ». « La sobriété dans la vie quotidienne, la discipline du travail intellectuel, la maîtrise des passions peuvent représenter les meilleures garanties pour une vie longue et heureuse ». Lorsqu'il veut donner une recette contre le vieillissement il cite Chevreul: « Modération en tout ».

Le prof. Gh. Marinescu a abordé clairement le rôle de la gérontologie sociale. Dès 1924 il a affirmé que: « les mesures d'hygiène et de prophylaxie individuelle et sociale . . . ont donné des résultats incontestables dans le prolongement moyen de la vie ». Après avoir rappelé le rôle des facteurs sociaux, des professions et des traumatismes psychiques liés à certaines formes d'activité, il conclut: « Je ne doute pas qu'avec les progrès de la médecine sociale, unis à ceux d'une saine éducation morale . . . les misères de la vieillesse ne seront plus si accablantes ». On voit donc que Marinescu a eu l'intuition du rôle des mesures médicales d'ordre social et de l'éducation des masses.

Ainsi qu'on peut le voir, il y a plus d'un demi-siècle depuis que le prof. Gh. Marinescu a tracé les grandes lignes du développement de la gérontologie. Il a relevé le rôle de la recherche fondamentale biologique, biochimique et biophysique; de la médecine prophylactique et curative ainsi que de la gérontologie sociale.

Son point de vue gérontologique s'appuie sur des recherches personnelles minutieuses, sur une conception matérialiste et dialectique des phénomènes de la vie et reflète un optimisme réaliste très réservé mais imprégné d'un profond humanisme.

ROMANIAN J. GERONT. GERIATRICS, 1981, 2, 1, p. 201

BOOK REVIEWS

PHARMACOLOGICAL INTERVENTION IN THE AGING PROCESS. Edited by Jay Roberts, Richard C. Adelman and Vincent J. Cristofalo, Plenum Press, New York — London, 1978, 348 pp.

The interrelationships between gerontology and pharmacology became ever more important for most of the specialists dealing with these fields. On the one hand, a better knowledge of the pharmacological agents, their metabolic action and the new experimental procedures contribute to a better understanding of the aging process, and on the other hand, the rapid progress recorded by geriatric and gerontologic researches promotes the knowledge and application on a larger scale of the new agents in the geriatric therapy as well as the explanation of the effects induced by the aging process on the action of the pharmaceutic substances.

Taking into account both the fundamental researches and clinical application, *Pharmacological intervention in the aging process* examines the general action ways of the pharmacological agents and their application in the geriatric clinic, proving scientifically the important potentialities of interaction and interference with the degenerative processes promoting and accompanying aging.

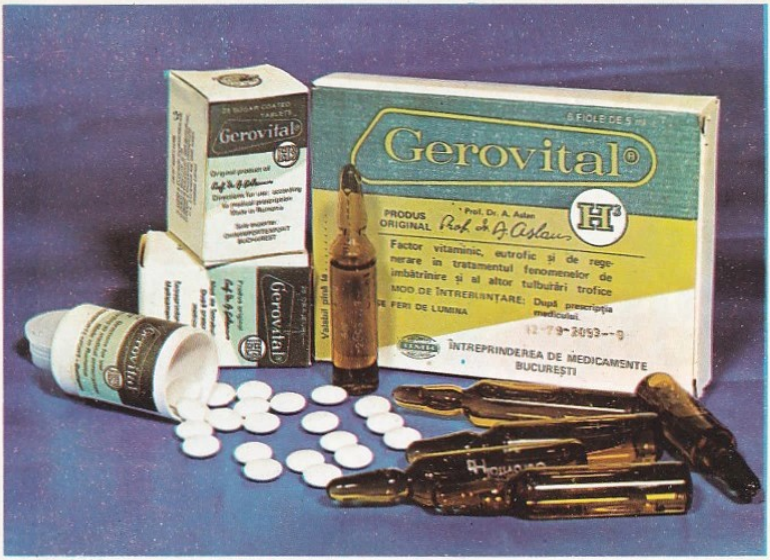
Examining the most important present data, the authors also postulate future possible investigations and experimental models concerning this question.

The book also presents the main reasons that account for the prescription of drug therapy in the elderly.

Th. Ionescu

original products of Prof. dr. A. Aslan

GEROVITAL H3



Vitamin, eutrophic factor and regenerator used in the treatment of aging phenomena and other trophic disorders.

VIALS AND SUGAR-COATED TABLETS

Indications:

- curative and prophylactic treatment of aging phenomena;
- treatment of trophic disorders;
- physical and psychic asthenia, depression, anxiety;
- neuritis, neuralgia;
- Parkinson's disease;
- degenerative rheumatism (spondylosis, arthrosis), rheumatoid polyarthritis, osteoporosis;
- dystrophies of the skin, nails and hair; neurodermitis; eczemas, alopecia, sclerodermia, psoriasis, vitiligo;
- vascular spasms;
- arteritis;
- bronchial asthma;
- gastric or duodenal ulcer

Supply:

- Boxes of 6, 12 and 25 vials of 5 ml
- Boxes of 100 vials of 5 ml
- Bottles of 25 sugar-coated tablets or capsules

Sole exporter: ICE "CHIMIMPORTEXPORT"

POB 525, Blvd Republicii 10, Bucharest, Romania, Telephone No. 16.06.36, Telex: 11184; 11697

Gerovital Prof. Dr. A. Aslan H3

Gerovital

Gerovital Prof. Dr. A. Aslan H3

Gerovital Prof. Dr. A. Aslan H3

H3

Prof. Dr. A. Aslan

Gerovital H3 hair lotion

For the care, regeneration and prevention of hair loss.

Indications: seborrhea, dandruff, pruritus, alopecia (baldness, partial hair loss), canities (white hair).

Sole exporter: ICE "CHIMIMPORTEXPORT"
POB 525, Blvd. Republicii 10,
Bucharest, Romania
Telephone No. 16.06.36. Telex: 11184; 11697

GEROVITAL
GEROVITAL

H3
cold
cream

Gerovital
Prof. Dr. A. Aslan H3

Prof. Dr.
Ana Aslan

CREMĂ DE FAȚĂ
Gerovital
Prof. Dr. A. Aslan H3

CRÈME DE BEAUTÉ
Gerovital
Prof. Dr. A. Aslan H3

H3

Gerovital
Prof. Dr. A. Aslan H3
FACE CREAM

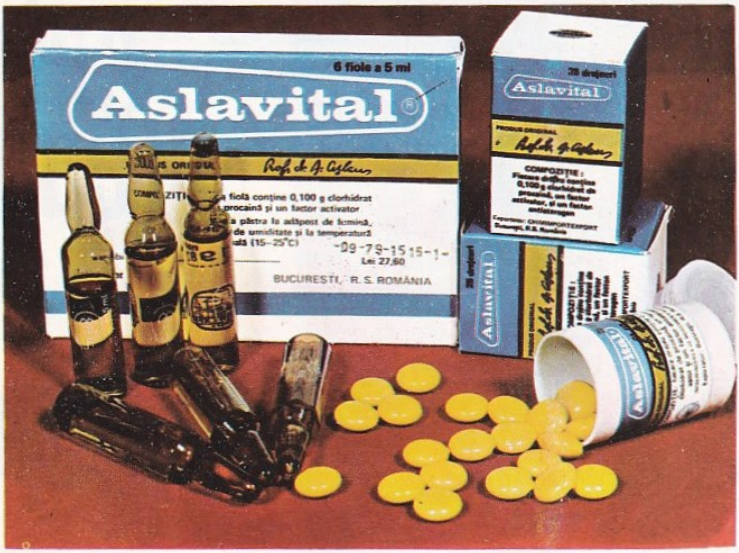
Ensures maintenance and nutrition of dry skin, normalizes the complexion, diminishes senile spots and acne, effaces wrinkles and other skin trophic disorders related to aging phenomena.

Indications:

care and regeneration of the skin; also efficient in mild burns

Sole exporter: ICE "CHIMIMPORTEXPORT" POB 525, Blvd. Republicii 10, Bucharest, Romania, Telephone No 16.06.36. Telex: 11184; 11697

ASLAVITAL



IMECO

Antiatherosclerotic, energising factor, active in the prophylaxis and treatment of aging phenomena of the central nervous system and cardiovascular apparatus.

Indications:

— prophylaxis and treatment of cerebral and cardio-vascular aging ;
— troubles of memory ;
— generalized, predominantly cerebral, coronary (angina pectoris), peripheral atherosclerosis ;
— prevention and control of thrombo-embolic accidents and post-hemorrhagic sequelae.
The drug is also indicated in children with psychosomatic undergrowth and encephalomyelitic sequelae.

Supply:

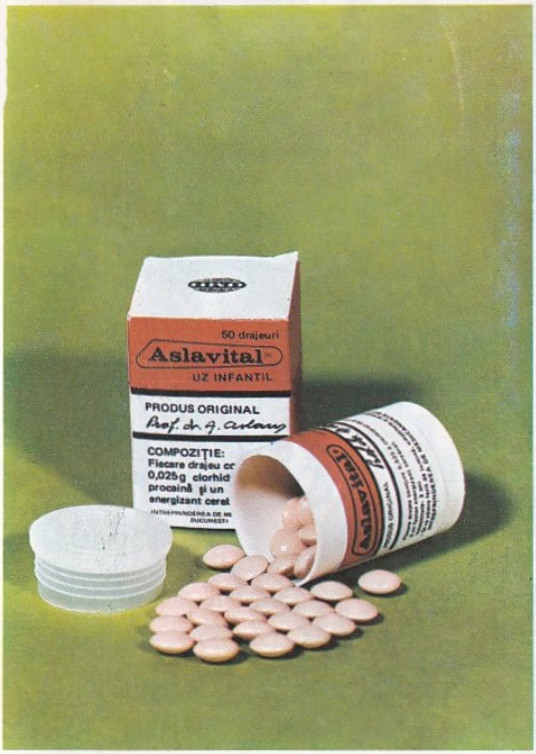
Boxes of 6, 12 and 100 vials of 5 ml.
Bottles of 25 sugar-coated tablets or capsules.

Sole exporter: ICE "CHIMIMPORTEXPORT"

POB 525, Blvd Republicii 10, Bucharest, Romania, Telephone No 16.06.36, Telex: 11184; 11697

original products of Prof. dr. A. Aslan

ASLAVITAL



for Children

EUTROPHIC REGENERATING FACTOR, WITH CELLULAR BIOCATALYTIC ACTION; IT ACTS PARTICULARLY ON THE NEURONAL METABOLISM. ESSENTIAL NUTRITIONAL FACTOR AND STIMULATOR OF GROWTH PROCESSES.

Original product of Prof. Dr. Ana Aslan

INDICATIONS

• Mentally deficient children • Mild and medium mental deficiency • Children with behavioral disturbances and defective integration in the school community • Impaired memory and concentration ability • Apathy, slowness, inertia, tendency to isolation, inferiority complex, difficult accomplishment of school tasks, failure to assert one's own will, take the initiative • Decreased resistance to physical and mental exercise • Encephalopathic sequelae.

SUPPLIED

Bottles of 50 sugar-coated pills.

EXPEDITOR

Chimimportexport

POB 525, BD. REPUBLICII, 10, BUCHAREST, ROMANIA
TELEPHONE: 16.06.36, TELEX 11184, 11697

ufrix

(isobutylhydroclorothiazine)

Diuretic agent with quick and persistent action; moderate potassium depletion, decreases arterial pressure.

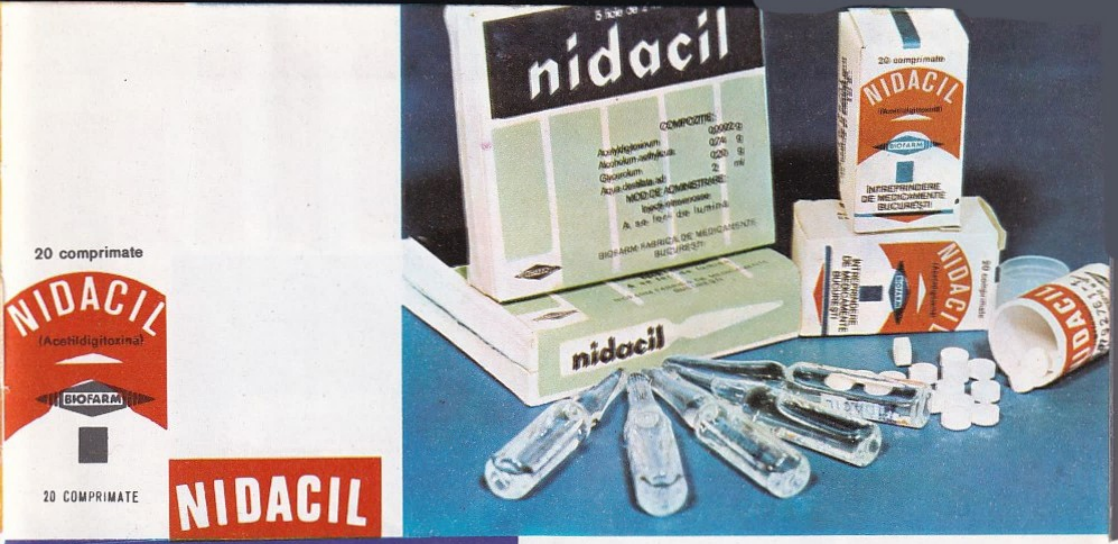
Indications: hydrosaline retention (without renal failure), cardiogenic oedemas, essential hypertension, cirrhosis with ascites, pregnacy with oedemas.

Contraindications: renal and hepatic failure; hypopotassemia.

Supply: tablets of 0.005 g.

Producer: *Drug Factory Bucharest, Romania.*

UMB



20 comprimate

NIDACIL

(Acetildigitoxina)

BIOFARM

20 COMPRIMATE

NIDACIL

5 fiole de 2 ml

nidacil

(acetyldigitoxin)

Indications:

all forms of myocardial failure with accelerated rhythm, atrial fibrillation, paroxysmal tachycardia, flutter.

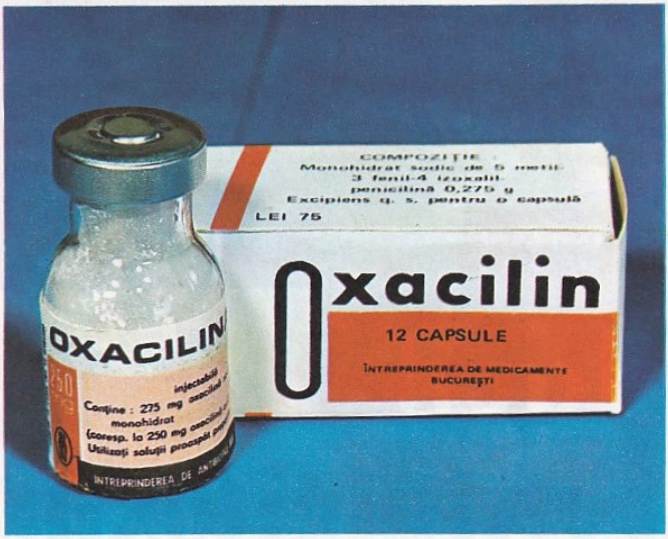
Digitaline-like cardiotonic. Positive inotropic action (increases myocardial contraction capacity), negative chronotropic action (slows down myocardial rhythm), improves coronary circulation.

Contraindications: acute decompensated cardiopathy (myocardia failure, , recent myocardial infarction), acute pulmonary oedema.
Not to be used when calcium is administered

Supply: Vials with injectable solution containing 0.0002 g acetyldigitoxir
Tablets containing 0.002 g acetyldigitoxin.
Solution of 0.050 g in 100 ml.
Suppositories.

Producer: Biofarm Factory, Bucharest, Romania

Oxacilin



Semisynthetic penicillin; acid- and penicillinase-resistant.

Indications: Infections produced by staphylococci resistant to other types of penicillin; cutaneous infections; respiratory infections, urinary infections, osteomyelitis

Contra-indications: Intolerance to penicillin.

Supply: capsules containing 0.275 g sodic oxacyline monohydrate.

Producer: Antibiotics Factory Iaşi, Romania.

SINAIA

At an altitude of 800 m above sea level lies the "Pearl of the Carpathians", a name by which this beautiful health-resort is also recorded.
Its microclimate is propitious to the therapy of different neuroses, depressive states, and hyperthyroidism.

A geriatric center on the precincts of Palace Hotel provides treatment with Gerovital H 3 and Aslavital according to Prof. Dr. Ana Aslan's method.

Otopeni

At a distance of some 17 kms from Bucharest, on the Ploiești motorway that goes to the mountain resorts of the Southern Carpathians, stands the "Otopeni" clinical section of the National Institute of Gerontology and Geriatrics in the midst of a beautiful 70 ha park.

Prof. Dr. Ana Aslan's treatment method with *Gerovital H3* and *Aslavital* is being applied for about ten years. The excellent accommodation and services, the quiet and picturesque ambient as well as the low altitude of the place recommend it to geriatric patients.

BĂILE HERCULANE

Herculane Spa (160 m altitude) is situated in the south-west of Romania, not far from the Iron Gate, in the picturesque valley of the Cerna river. The resort was recorded as early as the time of the Roman Empire for its curative properties and mild climate with Mediterranean influences. It is especially recommended for locomotive ailments (arthrosis, spondylosis, etc.), but also for affections of the peripheral nervous system, of the digestive tract (colitis, hypoacid gastritis, etc.), of the respiratory apparatus (chronic bronchitis), and for gynecological treatment.

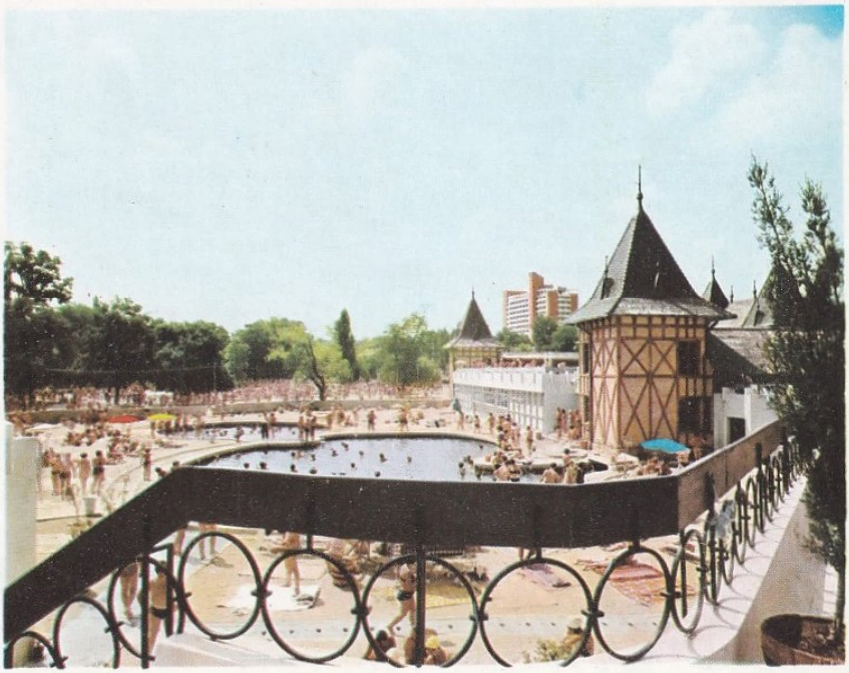
A geriatric section staffed with physicians from the National Institute of Gerontology and Geriatrics provides a Gerovital H3 and Aslavital therapy according to Prof. Dr. Ana Aslan's method. Open all the year round.

BAILE FELIX

In the north-west of Romania, close to Oradea city, lies Felix Spa.

Its microclimate and low altitude are indicated for various neurotic states, but what has made the resort famous is its treatment center against various types of rheumatism.

A geriatric section, where treatments with Gerovital H3 and Aslavital according to Prof. Dr. Ana Aslan's method are administered by physicians from the National Institute of Gerontology and Geriatrics, is open all the year round.



COUNSEL TO AUTHORS

The Romanian Journal of Gerontology and Geriatrics publishes original papers, reports, syntheses and reviews dealing with creative research in gerontology and geriatrics. The papers should be written in one of the following languages: English, French, German, Italian.

1. The size of the manuscript (including illustrations, tables, references and summaries) should not exceed 10 pages. Reports and syntheses should not outnumber 15 pages.

The manuscript should be typed with double-spacing (31 lines per page). Two summaries containing a maximum of 15 lines, one written in a different language than the manuscript, should be included.

Illustrations will be considered as pages (one page = 150 cm^2).

2. The paper should be consistent with the following plan: title; authors' names; the name of the institute where the authors have conducted their research work and the respective address; summary (in the manuscript language); introduction; material and method; results; discussion; conclusions; summary (in a different language); references.

3. Figures should be drawn on tracing, white or scale paper, in India ink, preferably the size intended for publication (1/1).

Legends should be typed with double-spacing on separate sheets, as included in the manuscript.

Whenever microphotographs are used, staining and × should be mentioned. The place of figures and microphotographs will be noted in the manuscript.

4. Tables should be typed with double-spacing on separate sheets. They will be placed at the end of the text; suggested location keyed to text.

5. References should be numbered in the text with parenthetic Arabic numerals, in order of occurrence. A double-spaced bibliography at the end of the paper will include:

a) for papers published in periodicals: author/s (initial/s of the first name, family name); full title of paper; title of publication according to usual abbreviations (cf. Index Medicus); volume; number; year; first and last page.

Example: A. Vasiliu, I. Popescu, *Peripheral circulation in the aged.* Romanian J. Geront. Geriatrics, **1**, *1*, 1980, 201—210.

b) for books, monographs, treatises: author/s; full title; publisher; town; year; page.

Romanian titles of papers will be translated into the language of the manuscript, with the indication (in Romanian).

References should be typed on a separate sheet.

6. All manuscripts meeting these standards should be addressed to:

The National Institute of Gerontology and Geriatrics
Editorial Board of the Romanian Journal of Gerontology and Geriatrics
Str. Mănăstirea Căldărușani No. 9, R-78178-București, România

PRINTED IN ROMANIA

EDITURA ACADEMIEI REPUBLICII SOCIALISTE ROMÂNIA
Calea Victoriei 125, R-79717-București, România, Sector 1, Tel. 50.76.80

FORTHCOMING PUBLICATIONS OF THE INSTITUTE

— a volume containing scientific papers on the prophylaxis and therapy with Gerovital H_3, published in Romania and abroad;

— a volume containing scientific papers on the therapy with Aslavital

ROMANIAN J. GERONT. GERIATRICS, 1981, 2, 1, BUCHAREST

Lei 25
$50 (price per year)